

COLCHINOL DERIVATIVES AS VASCULAR DAMAGING AGENTS

The present invention relates to vascular damaging agents, in particular to the use of compounds of the invention in the manufacture of medicaments for use in the production of antiangiogenic effects in warm-blooded animals such as humans, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds as active ingredient, to methods for the treatment of disease states associated with angiogenesis and to the use of such compounds as medicaments.

Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Formation of new vasculature by angiogenesis is a key pathological feature of several diseases (J. Folkman, New England Journal of Medicine 333, 1757-1763 (1995)). For example, for a solid tumour to grow it must develop its own blood supply upon which it depends critically for the provision of oxygen and nutrients; if this blood supply is mechanically shut off the tumour undergoes necrotic death. Neovascularisation is also a clinical feature of skin lesions in psoriasis, of the invasive pannus in the joints of rheumatoid arthritis patients and of atherosclerotic plaques. Retinal neovascularisation is pathological in macular degeneration and in diabetic retinopathy.

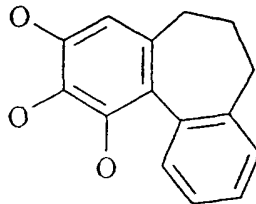
Reversal of neovascularisation by damaging the newly-formed vascular endothelium is expected to have a beneficial therapeutic effect. The present invention is based on the discovery of tricyclic compounds that surprisingly specifically damage newly formed vasculature without affecting the normal, established vascular endothelium of the host species, a property of value in the treatment of disease states associated with angiogenesis such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation.

Compounds of the present invention are colchinel derivatives. Colchinel derivatives for example *N*-acetyl-colchinel are known. Anti-tumour effects have been noted on animal

models (see for example - Jnl. Natl. Cancer Inst. 1952, 13, 379-392). However, the effect studied was that of gross damage (haemorrhage, softening and necrosis) and there is no suggestion of treatment of inappropriate angiogenesis by destruction of neovasculature.

A search of Chemical Abstracts (post 1955) based on the substructure:

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revealed a number of colchicinol related structures. To the extent that any of these compounds have been studied for anti-cancer activity it is because tubulin-binding agents like colchicinol might be expected to be anti-mitotic and therefore to have a direct effect on tumour cells. Some compounds which bind tubulin have been shown to have anti-vascular effects when given at their maximum tolerated dose (MTD) (S.A. Hill et al. Eur. J Cancer, 29A, 1320-1324 (1993)) but other tubulin-binding agents have no vascular-damaging activity even when administered at the MTD, for example docetaxel (Lancet, 1994, 344, 1267-1271). Based on this information and in the course of the work on the present invention, the issue of the relevance of tubulin-binding properties to possible effectiveness as anti-vascular agent was studied but no predictability was found. No correlation between the potency of tubulin interaction and effectiveness as an anti-vascular agent is apparent. Certain compounds structurally related to those of the present invention but not of the present invention, have been found to have a therapeutic window (ratio of MTD to minimum effective dose (MED)) too small for potential clinical effectiveness.

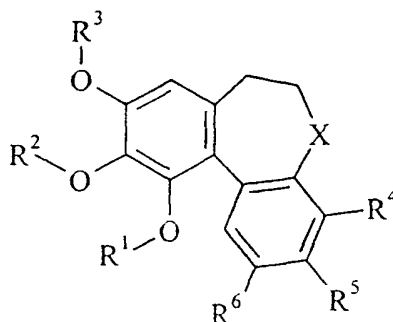
The presence of tubulin-binding properties is then not predictive for antitumour activity. Compounds which have strong tubulin-binding activity give rise to antimitotic effects *in vivo*. The effects of this are most noticeable on proliferating tissue and give rise to undesirable effects, for example on the proliferative tissue of the gut and bone marrow. Compounds which have vascular damaging activity but weak tubulin-binding activity would therefore be useful in the treatment of diseases involving angiogenesis.

It is believed, though this is not limiting on the invention, that the use of compounds of the invention damages newly-formed vasculature, for example the vasculature of tumours.

thus effectively reversing the process of angiogenesis as compared to known anti-angiogenic agents which tend to be less effective once the vasculature has formed.

According to one aspect of the present invention there is provided the use of a compound of the formula I:

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(I)

wherein

X is

10 -C(O)-, -C(S)-, -C=NOH, or -CH(R⁷)- wherein R⁷ is hydrogen, hydroxy, C₁₋₇alkoxy, -OR⁸ or -NR⁸R⁹ (wherein R⁸ is a group -Y¹R¹⁰ (wherein Y¹ is a direct bond, -C(O)-, -C(S)-, -S-, -C(O)O-, -C(O)NR¹¹-, -SO₂- or -SO₂NR¹²- (wherein R¹¹ and R¹², which may be the same or different, each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁰ is selected from one of the following nine groups:

15 1) hydrogen, C₁₋₇alkyl, C₃₋₇cycloalkyl, C₁₋₄alkylY⁸C₁₋₄alkyl wherein Y⁸ is as defined hereinafter, or phenyl,

(which alkyl, cycloalkyl, alkylY⁸alkyl or phenyl group may bear one or more substituents selected from:

20 halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, carboxy, carbamoyl, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, phenyl, nitro, sulphate, phosphate,

Z¹ (wherein Z¹ represents a 5-6 membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

25 oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄aminoalkyl, C₁₋₇alkanoyl, cyanoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl and Z² (wherein Z² is a 5-6-membered saturated

heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

- 5 oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄aminoalkyl, C₁₋₇alkanoyl, cyanoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl and C₁₋₄alkylsulphonylC₁₋₄alkyl)),
- C₁₋₄alkylZ¹ (wherein Z¹ is as defined hereinbefore), and
- a group -Y²R¹³ (wherein Y² is -NR¹⁴C(O)- or -O-C(O)- (wherein R¹⁴ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹³ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a
- 10 group R¹⁵ wherein R¹⁵ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy,
- 15 carboxy, cyano, -CONR¹⁶R¹⁷ and -NR¹⁸COR¹⁹ (wherein R¹⁶, R¹⁷, R¹⁸ and R¹⁹, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- 2) R¹⁵ wherein R¹⁵ is as defined hereinbefore;
- 3) C₂₋₇alkenylR¹⁵ (wherein R¹⁵ is as defined hereinbefore);
- 20 4) C₃₋₇alkynylR¹⁵ (wherein R¹⁵ is as defined hereinbefore));
- 5) Z¹ (wherein Z¹ is as defined hereinbefore);
- 6) C₁₋₇alkylZ¹ (wherein Z¹ is as defined hereinbefore);
- 7) C₁₋₇alkylY⁸Z¹ (wherein Z¹ is as defined hereinbefore and Y⁸ is -C(O)-, -NR⁵⁹C(O)-, -NR⁵⁹C(O)C₁₋₄alkyl-, -C(O)NR⁶⁰- or -C(O)NR⁶⁰C₁₋₄alkyl-, (wherein R⁵⁹ and R⁶⁰, which may be
- 25 the same or different, each represents hydrogen, C₁₋₃alkyl, C₁₋₃hydroxyalkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- 8) (C₁₋₇alkyl)_cY⁹Z³ (wherein c is 0 or 1, Z³ is an amino acid group and Y⁹ is a direct bond, -C(O)- or -NR⁶¹- (wherein R⁶¹ is hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl)); and
- 9) C₁₋₇alkylR¹⁵ (wherein R¹⁵ is as defined hereinbefore);
- 30 and R⁹ is hydrogen, C₁₋₇alkyl or C₃₋₇cycloalkyl, which alkyl or cycloalkyl group may bear one or more substituents selected from C₁₋₄alkoxy and phenyl);

R^1 , R^2 and R^3 are each independently

hydrogen, PO_3H_2 , sulphate, C_{3-7} cycloalkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{1-7} alkanoyl, a group $\text{R}^{20}\text{C}_{1-7}$ alkyl (wherein R^{20} is phenyl which may bear one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} aminoalkyl and C_{1-4} hydroxyalkoxy), C_{1-7} alkyl or C_{1-7} alkylsulphonyl

- 5 (which alkyl or alkylsulphonyl group may bear one or more substituents selected from: halogeno, amino, C_{1-4} alkylamino, $\text{di}(\text{C}_{1-4}$ alkyl)amino, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-\text{Y}^2\text{R}^{21}$ (wherein Y^2 is $-\text{NR}^{22}\text{C}(\text{O})-$ or $-\text{O}-\text{C}(\text{O})-$ (wherein R^{22} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{21} is C_{1-7} alkyl, C_{3-7} cycloalkyl or a group R^{23} wherein R^{23} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-\text{CONR}^{24}\text{R}^{25}$ and $-\text{NR}^{26}\text{COR}^{27}$ (wherein R^{24} , R^{25} , R^{26} and R^{27} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));
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with the proviso that at least two of R^1 , R^2 and R^3 are C_{1-7} alkyl;

- 20 R^4 , R^5 and R^6 are each independently selected from: hydrogen, $-\text{OPO}_3\text{H}_2$, phosphonate, cyano, halogeno, nitro, amino, carboxy, carbamoyl, hydroxy, C_{1-7} alkoxy, C_{1-7} alkanoyl, C_{1-7} thioalkoxy, C_{1-7} alkyl, (which alkyl group may bear one or more substituents selected from: halogeno, amino, C_{1-4} alkylamino, $\text{di}(\text{C}_{1-4}$ alkyl)amino, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy, phenyl, sulphate, phosphate and a group $-\text{Y}^3\text{R}^{28}$ (wherein Y^3 is $-\text{NR}^{29}\text{C}(\text{O})-$ or $-\text{O}-\text{C}(\text{O})-$ (wherein R^{29} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{28} is C_{1-7} alkyl, C_{3-7} cycloalkyl or a group R^{30} wherein R^{30} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-\text{CONR}^{24}\text{R}^{25}$ and $-\text{NR}^{26}\text{COR}^{27}$ (wherein R^{24} , R^{25} , R^{26} and R^{27} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));
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₄hydroxyalkoxy, carboxy, cyano, -CONR³¹R³² and -NR³¹COR³² (wherein R³¹, R³², R³³ and R³⁴, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl))), and

a group -Y⁴R³⁵

- 5 (wherein Y⁴ is -C(O)-, -OC(O)-, -O-, -SO-, -SO₂-, -OSO₂-, -NR³⁶-, -C₁₋₄alkylNR³⁶-, -C₁₋₄alkylC(O)-, -NR³⁷C(O)-, -OC(O)O-, -C(O)NR³⁸- or -NR³⁹C(O)O- (wherein R³⁶, R³⁷, R³⁸ and R³⁹, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and

- 10 R³⁵ is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, hydroxy, amino, C₁₋₇alkyl, C₁₋₇alkoxy, C₁₋₇alkanoyl, C₁₋₇alkylamino, di(C₁₋₇alkyl)amino, aminoC₁₋₇alkylamino, C₁₋₇alkylaminoC₁₋₇alkylamino, C₁₋₇alkanoylaminoC₁₋₇alkyl, di(C₁₋₇alkyl)aminoC₁₋₇alkylamino, C₁₋₇alkylphosphate, C₁₋₇alkylphosphonate, C₁₋₇alkylcarbamoylC₁₋₇alkyl,

- 15 (which alkyl, alkoxy, alkanoyl, alkylamino, dialkylamino, aminoalkylamino, alkylaminoalkylamino, alkanoylaminoalkyl, dialkylaminoalkylamino, alkylphosphate, alkylphosphonate or alkylcarbamoylalkyl, may bear one or more substituents selected from:

- halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -Y⁵R⁴⁰ (wherein Y⁵ is -NR⁴¹C(O)-, -C(O)NR⁴²-, -C(O)-O- or -O-C(O)- (wherein R⁴¹ and R⁴² which may be the same or different each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁴⁰ is C₁₋₇alkyl, C₃₋₇cycloalkyl, carboxyC₁₋₇alkyl or a group R⁴³ wherein R⁴³ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR⁴⁴R⁴⁵ and -NR⁴⁶COR⁴⁷ (wherein R⁴⁴, R⁴⁵, R⁴⁶ and R⁴⁷, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl))),
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R⁴⁸ (wherein R⁴⁸ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from

- 5 hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, di(C₁₋₄hydroxyalkyl)aminoC₁₋₄alkyl, di(C₁₋₄aminoalkyl)aminoC₁₋₄alkyl, C₁₋₄hydroxyalkoxy, carboxy, C₁₋₄carboxyalkyl, phenyl, cyano, -CONR⁴⁹R⁵⁰, -NR⁵¹COR⁵² (wherein R⁴⁹, R⁵⁰, R⁵¹ and R⁵², which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and C₁₋₄alkylR⁵³ (wherein R⁵³ is as defined hereinafter),

C₁₋₇alkylR⁴⁸ (wherein R⁴⁸ is as defined hereinbefore),

R⁵³ (wherein R⁵³ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

- 15 oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄carboxyalkyl, C₁₋₄aminoalkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl and R⁵⁴ (wherein R⁵⁴ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

- 20 oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl and C₁₋₄alkylsulphonylC₁₋₄alkyl)), or

(CH₂)_aY⁶(CH₂)_bR⁵³ (wherein R⁵³ is as defined hereinbefore, a is 0, or an integer 1-4, b is 0 or an integer 1-4 and Y⁶ represents a direct bond, -O-, -C(O)-, -NR⁵⁵-, -NR⁵⁶C(O)- or -C(O)NR⁵⁷- (wherein R⁵⁵, R⁵⁶, and R⁵⁷, which may be the same or different, each represents

- 25 hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), and wherein one or more of the (CH₂)_a or (CH₂)_b groups may bear one or more substituents selected from hydroxy, amino and halogeno));

with the proviso that R⁵ is not hydroxy, alkoxy, substituted alkoxy (wherein R⁵ is Y⁴R³⁵ and Y⁴ is -O- and R³⁵ is C₁₋₇alkyl bearing one or more substituents selected from the list given

- 30 hereinbefore), -OPO₃H₂, -O-C₁₋₇alkanoyl or benzyloxy;

and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof in the manufacture of a medicament for use in the production of a vascular damaging effect in warm-blooded animals such as humans.

According to a further aspect of the present invention there is provided the use of a
 5 compound of the formula I as defined hereinbefore and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof in the manufacture of a medicament for use in the production of a vascular damaging effect at less than the maximum tolerated dose in warm-blooded animals such as humans.

Conveniently X is -C(O)-, -C(S)- or -CH(R⁷)- wherein R⁷ is hydrogen, hydroxy, -OR⁸ or -
 10 NR⁸R⁹ (wherein R⁸ is a group -Y¹R¹⁰ (wherein Y¹ is a direct bond, -C(O)-, -C(S)-, -S-, -C(O)O-, -C(O)NR¹¹-, -SO₂- or -SO₂NR¹²- (wherein R¹¹ and R¹², which may be the same or different, each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁰ is selected from one of the following seven groups:

1) hydrogen, C₁₋₇alkyl, C₃₋₇cycloalkyl, C₁₋₄alkylY⁸C₁₋₄alkyl wherein Y⁸ is as defined

15 hereinafter, or phenyl,

(which alkyl, cycloalkyl, alkylY⁸alkyl or phenyl group may bear one or more substituents selected from:

halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, carboxy, carbamoyl, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, phenyl, nitro, sulphate, phosphate,

20 Z¹ (wherein Z¹ represents a 5-6 membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋

25 ₄aminoalkyl, C₁₋₇alkanoyl, cyanoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋

₄alkylsulphonylC₁₋₄alkyl and Z² (wherein Z² is a 5-6-membered saturated

heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms,

selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

30 oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋

₄aminoalkyl, C₁₋₇alkanoyl, cyanoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl and C₁₋

₄alkylsulphonylC₁₋₄alkyl)),

- $C_{1-4}alkylZ^1$ (wherein Z^1 is as defined hereinbefore), and
 a group $-Y^2R^{13}$ (wherein Y^2 is $-NR^{14}C(O)-$ or $-O-C(O)-$ (wherein R^{14} represents
 hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{13} is $C_{1-7}alkyl$, $C_{3-7}cycloalkyl$ or a
 group R^{15} wherein R^{15} is a 5-10-membered aromatic heterocyclic group (linked via
 5 carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S,
 aromatic heterocyclic group may bear one or more substituents selected from hydroxy,
 nitro, halogeno, amino, $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, $C_{1-4}alkoxy$, $C_{1-4}hydroxyalkyl$, C_{1-4}
 aminoalkyl, $C_{1-4}alkylamino$, $C_{1-4}hydroxyalkoxy$, carboxy, cyano, $-CONR^{16}R^{17}$ and $-$
 $NR^{18}COR^{19}$ (wherein R^{16} , R^{17} , R^{18} and R^{19} , which may be the same or different, each
 10 represents hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$));
- 2) R^{15} wherein R^{15} is as defined hereinbefore;
- 3) Z^1 (wherein Z^1 is as defined hereinbefore);
- 4) $C_{1-7}alkylZ^1$ (wherein Z^1 is as defined hereinbefore);
- 5) $C_{1-7}alkylY^8Z^1$ (wherein Z^1 is as defined hereinbefore and Y^8 is $-C(O)-$, $-NR^{59}C(O)-$, $-$
 15 $NR^{59}C(O)C_{1-4}alkyl-$, $-C(O)NR^{60}-$ or $-C(O)NR^{60}C_{1-4}alkyl-$, (wherein R^{59} and R^{60} , which may be
 the same or different, each represents hydrogen, $C_{1-3}alkyl$, $C_{1-3}hydroxyalkyl$ or $C_{1-3}alkoxyC_{2-3}$
 $alkyl$));
- 6) $(C_{1-7}alkyl)_cY^9Z^3$ (wherein c is 0 or 1, Z^3 is an amino acid group and Y^9 is a direct bond, $-$
 $C(O)-$ or $-NR^{61}-$ (wherein R^{61} is hydrogen, $C_{1-3}alkyl$ or $C_{1-3}alkoxyC_{2-3}alkyl$)); and
- 20 7) $C_{1-7}alkylR^{15}$ (wherein R^{15} is as defined hereinbefore));
- and R^9 is hydrogen, $C_{1-7}alkyl$ or $C_{3-7}cycloalkyl$, which alkyl or cycloalkyl group may bear one
 or more substituents selected from $C_{1-4}alkoxy$ and phenyl).
- Advantageously X is $-CH(R^7)-$ wherein R^7 is $-OR^8$ or $-NR^8R^9$ (wherein R^8 is a group $-Y^1R^{10}$
 (wherein Y^1 is $-C(O)-$, $-C(O)O-$ or $-C(O)NR^{11}-$ (wherein R^{11} represents hydrogen, $C_{1-3}alkyl$ or
 25 $C_{1-3}alkoxyC_{2-3}alkyl$) and R^{10} is as defined hereinbefore) and R^9 is as defined hereinbefore).
- Preferably X is $-CH(R^7)-$ wherein R^7 is $-OR^8$ or $-NR^8R^9$ (wherein R^8 is a group $-Y^1R^{10}$
 (wherein Y^1 is $-C(O)-$ or $-C(O)O-$ and R^{10} is as defined hereinbefore) and R^9 is as defined
 hereinbefore).
- In one embodiment of the present invention preferably X is $-C(O)-$, $-CH_2-$, $-CH(OH)-$ or $-$
 30 $CH(NHC(O)CH_3)-$.
- In one embodiment of the present invention more preferably X is $-CH(NHC(O)CH_3)-$.
- Conveniently R^1 , R^2 and R^3 are each independently

hydrogen, PO_3H_2 , sulphate, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{1-7} alkanoyl, C_{1-7} alkylsulphonyl or a group $\text{R}^{20}\text{C}_{1-7}$ alkyl (wherein R^{20} is phenyl which may bear one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} aminoalkyl and C_{1-4} hydroxyalkoxy); with the proviso that at least two of R^1 , R^2 and R^3 are C_{1-7} alkyl.

5 Preferably R^1 , R^2 and R^3 are each independently C_{1-4} alkyl.

More preferably R^1 , R^2 and R^3 are each methyl.

Conveniently R^4 is

hydrogen, cyano, halogeno, nitro, amino, hydroxy, C_{1-7} alkoxy, C_{1-7} thioalkoxy, C_{1-7} alkanoyl or C_{1-7} alkyl,

10 (which alkyl group may bear one or more substituents selected from

halogeno, amino, C_{1-4} alkylamino, $\text{di}(\text{C}_{1-4}$ alkyl)amino, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-\text{Y}^3\text{R}^{28}$ (wherein Y^3 is $-\text{NR}^{29}\text{C}(\text{O})-$ or $-\text{O}-\text{C}(\text{O})-$ (wherein R^{29} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{28} is C_{1-7} alkyl, C_{3-7} cycloalkyl or a group R^{30} wherein R^{30} is a phenyl group or a 5-10-membered

15 aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-\text{CONR}^{31}\text{R}^{32}$ and $-\text{NR}^{31}\text{COR}^{32}$ (wherein R^{31} , R^{32} , R^{33} and R^{34} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl))).

20 Preferably R^4 is hydrogen, hydroxy, halogeno, cyano, amino or C_{1-7} alkanoyl.

More preferably R^4 is hydrogen.

25 Conveniently R^5 and R^6 are each independently selected from:

hydrogen, $-\text{OPO}_3\text{H}_2$, phosphonate, cyano, halogeno, nitro, amino, carboxy, carbamoyl, hydroxy, C_{1-7} alkoxy, C_{1-7} alkanoyl, C_{1-7} thioalkoxy, C_{1-7} alkyl,

(which alkyl group may bear one or more substituents selected from:

halogeno, amino, C_{1-4} alkylamino, $\text{di}(\text{C}_{1-4}$ alkyl)amino, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy,

30 phenyl, sulphate, phosphate and a group $-\text{Y}^3\text{R}^{28}$ (wherein Y^3 is $-\text{NR}^{29}\text{C}(\text{O})-$ or $-\text{O}-\text{C}(\text{O})-$ (wherein R^{29} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{28} is C_{1-7} alkyl, C_{3-7} cycloalkyl or a group R^{30} wherein R^{30} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-\text{CONR}^{31}\text{R}^{32}$ and $-\text{NR}^{31}\text{COR}^{32}$ (wherein R^{31} , R^{32} , R^{33} and R^{34} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl))).

cycloalkyl or a group R^{30} wherein R^{30} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-\text{CONR}^{31}\text{R}^{32}$ and $-\text{NR}^{31}\text{COR}^{32}$ (wherein R^{31} , R^{32} , R^{33} and R^{34} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl)); and

a group $-\text{Y}^4\text{R}^{35}$

(wherein Y^4 is $-\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{O}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{OSO}_2-$, $-\text{NR}^{36}-$, $-\text{C}_{1-4}\text{alkylNR}^{36}-$, $-\text{C}_{1-4}\text{alkylC}(\text{O})-$, $-\text{NR}^{37}\text{C}(\text{O})-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NR}^{38}-$ or $-\text{NR}^{39}\text{C}(\text{O})\text{O}-$ (wherein R^{36} , R^{37} , R^{38} and R^{39} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and

R^{35} is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, hydroxy, amino, C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkanoyl, C_{1-7} alkylamino, $\text{di}(C_{1-7}\text{alkyl})\text{amino}$, $\text{aminoC}_{1-7}\text{alkylamino}$, $\text{C}_{1-7}\text{alkylaminoC}_{1-7}\text{alkylamino}$, $\text{C}_{1-7}\text{alkanoylaminoC}_{1-7}\text{alkyl}$, $\text{di}(C_{1-7}\text{alkyl})\text{aminoC}_{1-7}\text{alkylamino}$, $\text{C}_{1-7}\text{alkylphosphate}$, $\text{C}_{1-7}\text{alkylphosphonate}$, $\text{C}_{1-7}\text{alkylcarbamoylC}_{1-7}\text{alkyl}$,

(which alkyl, alkoxy, alkanoyl, alkylamino, dialkylamino, aminoalkylamino,

alkylaminoalkylamino, alkanoylaminoalkyl, dialkylaminoalkylamino, alkylphosphate, alkylphosphonate or alkylcarbamoylalkyl, may bear one or more substituents selected from:

halogeno, amino, C_{1-4} alkylamino, $\text{di}(C_{1-4}\text{alkyl})\text{amino}$, hydroxy, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-\text{Y}^5\text{R}^{40}$ (wherein Y^5 is $-\text{NR}^{41}\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{42}-$, $-\text{C}(\text{O})-\text{O}-$ or $-\text{O}-\text{C}(\text{O})-$ (wherein R^{41} and R^{42} which may be the same or different each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{40} is C_{1-7} alkyl, C_{3-7} cycloalkyl, $\text{carboxyC}_{1-7}\text{alkyl}$ or a group R^{43} wherein R^{43} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-\text{CONR}^{44}\text{R}^{45}$ and $-\text{NR}^{44}\text{COR}^{45}$ (wherein R^{44} , R^{45} , R^{46} , R^{47} , R^{48} , R^{49} , R^{50} , R^{51} , R^{52} , R^{53} , R^{54} , R^{55} , R^{56} , R^{57} , R^{58} , R^{59} , R^{60} , R^{61} , R^{62} , R^{63} , R^{64} , R^{65} , R^{66} , R^{67} , R^{68} , R^{69} , R^{70} , R^{71} , R^{72} , R^{73} , R^{74} , R^{75} , R^{76} , R^{77} , R^{78} , R^{79} , R^{80} , R^{81} , R^{82} , R^{83} , R^{84} , R^{85} , R^{86} , R^{87} , R^{88} , R^{89} , R^{90} , R^{91} , R^{92} , R^{93} , R^{94} , R^{95} , R^{96} , R^{97} , R^{98} , R^{99} , R^{100} , R^{101} , R^{102} , R^{103} , R^{104} , R^{105} , R^{106} , R^{107} , R^{108} , R^{109} , R^{110} , R^{111} , R^{112} , R^{113} , R^{114} , R^{115} , R^{116} , R^{117} , R^{118} , R^{119} , R^{120} , R^{121} , R^{122} , R^{123} , R^{124} , R^{125} , R^{126} , R^{127} , R^{128} , R^{129} , R^{130} , R^{131} , R^{132} , R^{133} , R^{134} , R^{135} , R^{136} , R^{137} , R^{138} , R^{139} , R^{140} , R^{141} , R^{142} , R^{143} , R^{144} , R^{145} , R^{146} , R^{147} , R^{148} , R^{149} , R^{150} , R^{151} , R^{152} , R^{153} , R^{154} , R^{155} , R^{156} , R^{157} , R^{158} , R^{159} , R^{160} , R^{161} , R^{162} , R^{163} , R^{164} , R^{165} , R^{166} , R^{167} , R^{168} , R^{169} , R^{170} , R^{171} , R^{172} , R^{173} , R^{174} , R^{175} , R^{176} , R^{177} , R^{178} , R^{179} , R^{180} , R^{181} , R^{182} , R^{183} , R^{184} , R^{185} , R^{186} , R^{187} , R^{188} , R^{189} , R^{190} , R^{191} , R^{192} , R^{193} , R^{194} , R^{195} , R^{196} , R^{197} , R^{198} , R^{199} , R^{200} , R^{201} , R^{202} , R^{203} , R^{204} , R^{205} , R^{206} , R^{207} , R^{208} , R^{209} , R^{210} , R^{211} , R^{212} , R^{213} , R^{214} , R^{215} , R^{216} , R^{217} , R^{218} , R^{219} , R^{220} , R^{221} , R^{222} , R^{223} , R^{224} , R^{225} , R^{226} , R^{227} , R^{228} , R^{229} , R^{230} , R^{231} , R^{232} , R^{233} , R^{234} , R^{235} , R^{236} , R^{237} , R^{238} , R^{239} , R^{240} , R^{241} , R^{242} , R^{243} , R^{244} , R^{245} , R^{246} , R^{247} , R^{248} , R^{249} , R^{250} , R^{251} , R^{252} , R^{253} , R^{254} , R^{255} , R^{256} , R^{257} , R^{258} , R^{259} , R^{260} , R^{261} , R^{262} , R^{263} , R^{264} , R^{265} , R^{266} , R^{267} , R^{268} , R^{269} , R^{270} , R^{271} , R^{272} , R^{273} , R^{274} , R^{275} , R^{276} , R^{277} , R^{278} , R^{279} , R^{280} , R^{281} , R^{282} , R^{283} , R^{284} , R^{285} , R^{286} , R^{287} , R^{288} , R^{289} , R^{290} , R^{291} , R^{292} , R^{293} , R^{294} , R^{295} , R^{296} , R^{297} , R^{298} , R^{299} , R^{300} , R^{301} , R^{302} , R^{303} , R^{304} , R^{305} , R^{306} , R^{307} , R^{308} , R^{309} , R^{310} , R^{311} , R^{312} , R^{313} , R^{314} , R^{315} , R^{316} , R^{317} , R^{318} , R^{319} , R^{320} , R^{321} , R^{322} , R^{323} , R^{324} , R^{325} , R^{326} , R^{327} , R^{328} , R^{329} , R^{330} , R^{331} , R^{332} , R^{333} , R^{334} , R^{335} , R^{336} , R^{337} , R^{338} , R^{339} , R^{340} , R^{341} , R^{342} , R^{343} , R^{344} , R^{345} , R^{346} , R^{347} , R^{348} , R^{349} , R^{350} , R^{351} , R^{352} , R^{353} , R^{354} , R^{355} , R^{356} , R^{357} , R^{358} , R^{359} , R^{360} , R^{361} , R^{362} , R^{363} , R^{364} , R^{365} , R^{366} , R^{367} , R^{368} , R^{369} , R^{370} , R^{371} , R^{372} , R^{373} , R^{374} , R^{375} , R^{376} , R^{377} , R^{378} , R^{379} , R^{380} , R^{381} , R^{382} , R^{383} , R^{384} , R^{385} , R^{386} , R^{387} , R^{388} , R^{389} , R^{390} , R^{391} , R^{392} , R^{393} , R^{394} , R^{395} , R^{396} , R^{397} , R^{398} , R^{399} , R^{400} , R^{401} , R^{402} , R^{403} , R^{404} , R^{405} , R^{406} , R^{407} , R^{408} , R^{409} , R^{410} , R^{411} , R^{412} , R^{413} , R^{414} , R^{415} , R^{416} , R^{417} , R^{418} , R^{419} , R^{420} , R^{421} , R^{422} , R^{423} , R^{424} , R^{425} , R^{426} , R^{427} , R^{428} , R^{429} , R^{430} , R^{431} , R^{432} , R^{433} , R^{434} , R^{435} , R^{436} , R^{437} , R^{438} , R^{439} , R^{440} , R^{441} , R^{442} , R^{443} , R^{444} , R^{445} , R^{446} , R^{447} , R^{448} , R^{449} , R^{450} , R^{451} , R^{452} , R^{453} , R^{454} , R^{455} , R^{456} , R^{457} , R^{458} , R^{459} , R^{460} , R^{461} , R^{462} , R^{463} , R^{464} , R^{465} , R^{466} , R^{467} , R^{468} , R^{469} , R^{470} , R^{471} , R^{472} , R^{473} , R^{474} , R^{475} , R^{476} , R^{477} , R^{478} , R^{479} , R^{480} , R^{481} , R^{482} , R^{483} , R^{484} , R^{485} , R^{486} , R^{487} , R^{488} , R^{489} , R^{490} , R^{491} , R^{492} , R^{493} , R^{494} , R^{495} , R^{496} , R^{497} , R^{498} , R^{499} , R^{500} , R^{501} , R^{502} , R^{503} , R^{504} , R^{505} , R^{506} , R^{507} , R^{508} , R^{509} , R^{510} , R^{511} , R^{512} , R^{513} , R^{514} , R^{515} , R^{516} , R^{517} , R^{518} , R^{519} , R^{520} , R^{521} , R^{522} , R^{523} , R^{524} , R^{525} , R^{526} , R^{527} , R^{528} , R^{529} , R^{530} , R^{531} , R^{532} , R^{533} , R^{534} , R^{535} , R^{536} , R^{537} , R^{538} , R^{539} , R^{540} , R^{541} , R^{542} , R^{543} , R^{544} , R^{545} , R^{546} , R^{547} , R^{548} , R^{549} , R^{550} , R^{551} , R^{552} , R^{553} , R^{554} , R^{555} , R^{556} , R^{557} , R^{558} , R^{559} , R^{560} , R^{561} , R^{562} , R^{563} , R^{564} , R^{565} , R^{566} , R^{567} , R^{568} , R^{569} , R^{570} , R^{571} , R^{572} , R^{573} , R^{574} , R^{575} , R^{576} , R^{577} , R^{578} , R^{579} , R^{580} , R^{581} , R^{582} , R^{583} , R^{584} , R^{585} , R^{586} , R^{587} , R^{588} , R^{589} , R^{590} , R^{591} , R^{592} , R^{593} , R^{594} , R^{595} , R^{596} , R^{597} , R^{598} , R^{599} , R^{600} , R^{601} , R^{602} , R^{603} , R^{604} , R^{605} , R^{606} , R^{607} , R^{608} , R^{609} , R^{610} , R^{611} , R^{612} , R^{613} , R^{614} , R^{615} , R^{616} , R^{617} , R^{618} , R^{619} , R^{620} , R^{621} , R^{622} , R^{623} , R^{624} , R^{625} , R^{626} , R^{627} , R^{628} , R^{629} , R^{630} , R^{631} , R^{632} , R^{633} , R^{634} , R^{635} , R^{636} , R^{637} , R^{638} , R^{639} , R^{640} , R^{641} , R^{642} , R^{643} , R^{644} , R^{645} , R^{646} , R^{647} , R^{648} , R^{649} , R^{650} , R^{651} , R^{652} , R^{653} , R^{654} , R^{655} , R^{656} , R^{657} , R^{658} , R^{659} , R^{660} , R^{661} , R^{662} , R^{663} , R^{664} , R^{665} , R^{666} , R^{667} , R^{668} , R^{669} , R^{670} , R^{671} , R^{672} , R^{673} , R^{674} , R^{675} , R^{676} , R^{677} , R^{678} , R^{679} , R^{680} , R^{681} , R^{682} , R^{683} , R^{684} , R^{685} , R^{686} , R^{687} , R^{688} , R^{689} , R^{690} , R^{691} , R^{692} , R^{693} , R^{694} , R^{695} , R^{696} , R^{697} , R^{698} , R^{699} , R^{700} , R^{701} , R^{702} , R^{703} , R^{704} , R^{705} , R^{706} , R^{707} , R^{708} , R^{709} , R^{710} , R^{711} , R^{712} , R^{713} , R^{714} , R^{715} , R^{716} , R^{717} , R^{718} , R^{719} , R^{720} , R^{721} , R^{722} , R^{723} , R^{724} , R^{725} , R^{726} , R^{727} , R^{728} , R^{729} , R^{730} , R^{731} , R^{732} , R^{733} , R^{734} , R^{735} , R^{736} , R^{737} , R^{738} , R^{739} , R^{740} , R^{741} , R^{742} , R^{743} , R^{744} , R^{745} , R^{746} , R^{747} , R^{748} , R^{749} , R^{750} , R^{751} , R^{752} , R^{753} , R^{754} , R^{755} , R^{756} , R^{757} , R^{758} , R^{759} , R^{760} , R^{761} , R^{762} , R^{763} , R^{764} , R^{765} , R^{766} , R^{767} , R^{768} , R^{769} , R^{770} , R^{771} , R^{772} , R^{773} , R^{774} , R^{775} , R^{776} , R^{777} , R^{778} , R^{779} , R^{780} , R^{781} , R^{782} , R^{783} , R^{784} , R^{785} , R^{786} , R^{787} , R^{788} , R^{789} , R^{790} , R^{791} , R^{792} , R^{793} , R^{794} , R^{795} , R^{796} , R^{797} , R^{798} , R^{799} , R^{800} , R^{801} , R^{802} , R^{803} , R^{804} , R^{805} , R^{806} , R^{807} , R^{808} , R^{809} , R^{810} , R^{811} , R^{812} , R^{813} , R^{814} , R^{815} , R^{816} , R^{817} , R^{818} , R^{819} , R^{820} , R^{821} , R^{822} , R^{823} , R^{824} , R^{825} , R^{826} , R^{827} , R^{828} , R^{829} , R^{830} , R^{831} , R^{832} , R^{833} , R^{834} , R^{835} , R^{836} , R^{837} , R^{838} , R^{839} , R^{840} , R^{841} , R^{842} , R^{843} , R^{844} , R^{845} , R^{846} , R^{847} , R^{848} , R^{849} , R^{850} , R^{851} , R^{852} , R^{853} , R^{854} , R^{855} , R^{856} , R^{857} , R^{858} , R^{859} , R^{860} , R^{861} , R^{862} , R^{863} , R^{864} , R^{865} , R^{866} , R^{867} , R^{868} , R^{869} , R^{870} , R^{871} , R^{872} , R^{873} , R^{874} , R^{875} , R^{876} , R^{877} , R^{878} , R^{879} , R^{880} , R^{881} , R^{882} , R^{883} , R^{884} , R^{885} , R^{886} , R^{887} , R^{888} , R^{889} , R^{890} , R^{891} , R^{892} , R^{893} , R^{894} , R^{895} , R^{896} , R^{897} , R^{898} , R^{899} , R^{900} , R^{901} , R^{902} , R^{903} , R^{904} , R^{905} , R^{906} , R^{907} , R^{908} , R^{909} , R^{910} , R^{911} , R^{912} , R^{913} , R^{914} , R^{915} , R^{916} , R^{917} , R^{918} , R^{919} , R^{920} , R^{921} , R^{922} , R^{923} , R^{924} , R^{925} , R^{926} , R^{927} , R^{928} , R^{929} , R^{930} , R^{931} , R^{932} , R^{933} , R^{934} , R^{935} , R^{936} , R^{937} , R^{938} , R^{939} , R^{940} , R^{941} , R^{942} , R^{943} , R^{944} , R^{945} , R^{946} , R^{947} , R^{948} , R^{949} , R^{950} , R^{951} , R^{952} , R^{953} , R^{954} , R^{955} , R^{956} , R^{957} , R^{958} , R^{959} , R^{960} , R^{961} , R^{962} , R^{963} , R^{964} , R^{965} , R^{966} , R^{967} , R^{968} , R^{969} , R^{970} , R^{971} , R^{972} , R^{973} , R^{974} , R^{975} , R^{976} , R^{977} , R^{978} , R^{979} , R^{980} , R^{981} , R^{982} , R^{983} , R^{984} , R^{985} , R^{986} , R^{987} , R^{988} , R^{989} , R^{990} , R^{991} , R^{992} , R^{993} , R^{994} , R^{995} , R^{996} , R^{997} , R^{998} , R^{999} , R^{1000} , R^{1001} , R^{1002} , R^{1003} , R^{1004} , R^{1005} , R^{1006} , R^{1007} , R^{1008} , R^{1009} , R^{1010} , R^{1011} , R^{1012} , R^{1013} , R^{1014} , R^{1015} , R^{1016} , R^{1017} , R^{1018} , R^{1019} , R^{1020} , R^{1021} , R^{1022} , R^{1023} , R^{1024} , R^{1025} , R^{1026} , R^{1027} , R^{1028} , R^{1029} , R^{1030} , R^{1031} , R^{1032} , R^{1033} , R^{1034} , R^{1035} , R^{1036} , R^{1037} , R^{1038} , R^{1039} , R^{1040} , R^{1041} , R^{1042} , R^{1043} , R^{1044} , R^{1045} , R^{1046} , R^{1047} , R^{1048} , R^{1049} , R^{1050} , R^{1051} , R^{1052} , R^{1053} , R^{1054} , R^{1055} , R^{1056} , R^{1057} , R^{1058} , R^{1059} , R^{1060} , R^{1061} , R^{1062} , R^{1063} , R^{1064}

₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR⁴⁴R⁴⁵ and -NR⁴⁶COR⁴⁷ (wherein R⁴⁴, R⁴⁵, R⁴⁶ and R⁴⁷, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl))),

- 5 R⁴⁸ (wherein R⁴⁸ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from

hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, di(C₁₋₄hydroxyalkyl)aminoC₁₋₄alkyl, di(C₁₋₄aminoalkyl)aminoC₁₋₄alkyl, C₁₋₄hydroxyalkoxy, carboxy, C₁₋₄carboxyalkyl, phenyl, cyano, -CONR⁴⁹R⁵⁰, -NR⁵¹COR⁵² (wherein R⁴⁹, R⁵⁰, R⁵¹ and R⁵², which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and C₁₋₄alkylR⁵³ (wherein R⁵³ is as defined hereinafter),

- 15 C₁₋₇alkylR⁴⁸ (wherein R⁴⁸ is as defined hereinbefore),
R⁵³ (wherein R⁵³ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

20 oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄carboxyalkyl, C₁₋₄aminoalkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl and R⁵⁴ (wherein R⁵⁴ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

25 oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl and C₁₋₄alkylsulphonylC₁₋₄alkyl)), or

- (CH₂)_aY⁶(CH₂)_bR⁵³ (wherein R⁵³ is as defined hereinbefore, a is 0, or an integer 1-4, b is 0 or an integer 1-4 and Y⁶ represents a direct bond, -O-, -C(O)-, -NR⁵⁵-, -NR⁵⁶C(O)- or -C(O)NR⁵⁷- (wherein R⁵⁵, R⁵⁶, and R⁵⁷, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), and wherein one or more of the (CH₂)_a or (CH₂)_b groups may bear one or more substituents selected from hydroxy, amino and halogeno));
- 30

with the proviso that R^5 is not hydroxy, alkoxy, substituted alkoxy (wherein R^5 is Y^4R^{35} and Y^4 is -O- and R^{35} is C_{1-7} alkyl bearing one or more substituents selected from the list given hereinbefore), - OPO_3H_2 , - $O-C_{1-7}$ alkanoyl or benzyloxy.

In another embodiment of the present invention conveniently R^5 and R^6 are each

5 independently selected from:

hydrogen, - OPO_3H_2 , cyano, halogeno, nitro, amino, carboxy, hydroxy, C_{1-7} alkoxy, C_{1-7} alkanoyl, C_{1-7} thioalkoxy, C_{1-7} alkyl,

(which alkyl group may bear one or more substituents selected from:

halogeno, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy,

10 phenyl, sulphate, phosphate and a group - Y^3R^{28} (wherein Y^3 is - $NR^{29}C(O)-$ or - $O-C(O)-$ (wherein R^{29} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{28} is C_{1-7} alkyl, C_{3-7} cycloalkyl or a group R^{30} wherein R^{30} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected

15 independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, - $CONR^{31}R^{32}$ and - $NR^{31}COR^{32}$ (wherein R^{31} , R^{32} , R^{33} and R^{34} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl))), and

20 a group - Y^4R^{35}

(wherein Y^4 is - $C(O)-$, - $OC(O)-$, -O-, -SO-, - SO_2- , - OSO_2- , - $NR^{36}-$, - $NR^{37}C(O)-$, - $OC(O)O-$, - $C(O)NR^{38}-$ or - $NR^{39}C(O)O-$ (wherein R^{36} , R^{37} , R^{38} and R^{39} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{35} is

25 a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkanoyl, amino C_{1-7} alkylamino, C_{1-7} alkylamino C_{1-7} alkylamino, di(C_{1-7} alkyl)amino C_{1-7} alkylamino, C_{1-7} alkylphosphate

(which alkyl, alkoxy, alkanoyl, aminoalkylamino, alkylaminoalkylamino,

dialkylaminoalkylamino, or alkylphosphate may bear one or more substituents

30 selected from:

halogeno, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy,

- phenyl, nitro, sulphate, phosphate and a group $-Y^5R^{40}$ (wherein Y^5 is $-NR^{41}C(O)-$, $-C(O)NR^{42}-$, $-C(O)-O-$ or $-O-C(O)-$ (wherein R^{41} and R^{42} which may be the same or different each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{40} is C_{1-7} alkyl, C_{3-7} cycloalkyl, carboxy C_{1-7} alkyl or a group R^{43} wherein R^{43} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-CONR^{44}R^{45}$ and $-NR^{46}COR^{47}$ (wherein R^{44} , R^{45} , R^{46} and R^{47} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl))), R^{48} (wherein R^{48} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, phenyl, cyano, $-CONR^{49}R^{50}$ and $-NR^{51}COR^{52}$ (wherein R^{49} , R^{50} , R^{51} and R^{52} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl)), or R^{53} (wherein R^{53} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} alkylsulphonyl C_{1-4} alkyl and R^{54} (wherein R^{54} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl and C_{1-4} alkylsulphonyl C_{1-4} alkyl))));

with the proviso that R^5 is not hydroxy, alkoxy, substituted alkoxy, $-OPO_3H_2$,

- $-O-C_{1-7}$ alkanoyl or benzyloxy.

Preferably R^6 is hydrogen, halogeno, amino, carboxy, hydroxy, C_{1-7} alkoxy or a group Y^4R^{35}

(wherein Y^4 is $-C(O)-$, $-O-$ or $-OSO_2-$ and R^{35} is C_{1-7} alkyl, C_{1-7} alkoxy (which alkyl or alkoxy may bear one or more substituents selected from halogeno), R^{48} (wherein R^{48} is a benzyl group) or R^{53} (wherein R^{53} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms selected independently from O, S and N)).

5 Particularly R^6 is hydrogen, $C(O)OCH_3$ or methoxy, especially $C(O)OCH_3$ or methoxy.

More preferably R^6 is hydrogen.

Preferably R^5 is hydrogen, halogeno, amino, carboxy, carbamoyl, C_{1-7} alkanoyl, C_{1-7} thioalkoxy, or

a group $-Y^4R^{35}$

10 (wherein Y^4 is $-C(O)-$, $-OC(O)-$, $-O-$, $-SO-$, $-OSO_2-$, $-NR^{36}-$, $-NR^{37}C(O)-$ or $-C(O)NR^{38}-$ (wherein R^{36} , R^{37} and R^{38} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{35} is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkanoyl, C_{1-7} alkanoylamino C_{1-7} alkyl,

15 (which alkyl, alkoxy, alkanoyl, alkanoylaminoalkyl may bear one or more substituents selected from:

halogeno, amino, hydroxy, carboxy, and a group $-Y^5R^{40}$ (wherein Y^5 is $-C(O)-O-$ or $O-C(O)-$ and R^{40} is C_{1-7} alkyl or a group R^{43} wherein R^{43} is a benzyl group),

20 R^{48} (wherein R^{48} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from

hydroxy, fluoro, amino, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino C_{1-4} alkyl, di(C_{1-4} hydroxyalkyl)amino C_{1-4} alkyl, 25 di(C_{1-4} aminoalkyl)amino C_{1-4} alkyl, C_{1-4} hydroxyalkoxy, carboxy, C_{1-4} carboxyalkyl, cyano, $-CONR^{49}R^{50}$, $-NR^{51}COR^{52}$ (wherein R^{49} , R^{50} , R^{51} and R^{52} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and C_{1-4} alkyl R^{53} (wherein R^{53} is as defined hereinafter),

C_{1-7} alkyl R^{48} (wherein R^{48} is as defined hereinbefore),

30 R^{53} (wherein R^{53} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, fluoro, chloro, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄carboxyalkyl, C₁₋₄aminoalkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl and R⁵⁴ (wherein R⁵⁴ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N,

5 which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl and C₁₋₄alkylsulphonyl(C₁₋₄alkyl)), or

(CH₂)_aY⁶(CH₂)_bR⁵³ (wherein R⁵³ is as defined hereinbefore, a is 0, or an integer 1-4, b is 0 or an integer 1-4 and Y⁶ represents a direct bond, -O-, -C(O)-, -NR⁵⁵-, -NR⁵⁶C(O)- or -C(O)NR⁵⁷- (wherein R⁵⁵, R⁵⁶, and R⁵⁷, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), and wherein one or more of the (CH₂)_a or (CH₂)_b groups may bear one or more substituents selected from hydroxy, amino and halogeno));

with the proviso that R⁵ is not alkoxy, substituted alkoxy (wherein R⁵ is Y⁴R³⁵ and Y⁴ is -O- and R³⁵ is C₁₋₇alkyl bearing one or more substituents selected from the list given hereinbefore), -O-C₁₋₇alkanoyl or benzyloxy.

Preferably R⁵³ is a group selected from morpholino, piperidinyl and piperazinyl which group may be substituted as hereinbefore defined.

Advantageous values for R⁵ include:

- 20 3-{{(2R)-2,6-diaminohexanoyl}amino}propanoyloxy (such as in Example 4),
 3-[(2-aminoacetyl)amino]propanoyloxy (such as in Example 5),
 2-morpholinoacetylaminomethoxy (such as in Example 38),
 2-carboxy-3,4,5-trihydroxytetrahydro-2H-pyran-6-yloxy (such as in Example 44),
 4-(4-methylpiperazin-1-ylmethyl)phenylcarbonyloxy (such as in Example 16),
 25 4-(morpholinomethyl)phenylcarbonyloxy (such as in Example 17),
 3-(4-methylpiperazin-1-ylcarbonyl)propanoyloxy (such as in Example 40),
 5-carboxypentanoyloxy (such as in Example 41),
 3-(4-carboxyphenyl)propanoyloxy (such as in Example 18) and
 (3R)-2-amino-3-hydroxypropanoylamino (such as in Example 28).

30 Another advantageous value for R⁵ is

(2S)-2-amino-5-[(2-nitroethanimidoyl)amino]pentanoylamino (such as in Example 52).

Preferred values for R⁵ include

3-{[(2*R*)-2,6-diaminohexanoyl]amino}propanoyloxy (such as in Example 4),
 3-[(2-aminoacetyl)amino]propanoyloxy (such as in Example 5),
 4-(4-methylpiperazin-1-ylmethyl)phenylcarbonyloxy (such as in Example 16),
 4-(morpholinomethyl)phenylcarbonyloxy (such as in Example 17),
 5 3-(4-methylpiperazin-1-ylcarbonyl)propanoyloxy (such as in Example 40),
 5-carboxypentanoyloxy (such as in Example 41),
 3-(4-carboxyphenyl)propanoyloxy (such as in Example 18) and
 (3*R*)-2-amino-3-hydroxypropanoylamino (such as in Example 28).

More preferred values for R⁵ include

- 10 4-(4-methylpiperazin-1-ylmethyl)phenylcarbonyloxy (such as in Example 16) and
 (3*R*)-2-amino-3-hydroxypropanoylamino (such as in Example 28).

In another embodiment of the present invention preferred values for R⁵ include alanylamino,
N-(benzyloxycarbonylalanyl)amino, and 4-(piperidino)piperidin-1-ylcarbonyloxy.

A more preferred value for R⁵ is alanylamino.

- 15 In another embodiment of the present invention particular values of R⁵ include amino, C₁,
 ,alkylamino and diC₁₋₇alkylamino, especially amino.

When R³⁵ is a sugar moiety it can be, for example a monosaccharide such as a glucuronyl,
 glucosyl or galactosyl group or a di- or trisaccharide.

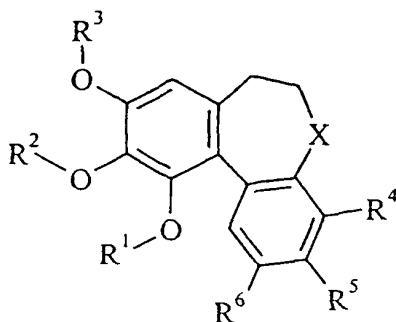
When R³⁵ is a sugar moiety glucuronyl or a derivative thereof is preferred.

- 20 When R³⁵ is a mono-, di-, tri- or tetra- peptide it is preferably derived from a natural alpha
 amino acid for example such as glycine, valine, lysine, alanine or serine.

In another embodiment of the present invention R³⁵ is an amino acid group derived from
 serine, threonine, arginine, glycine, alanine, β-alanine or lysine.

According to another aspect of the present invention there is provided the use of a

- 25 compound of the formula I:



(I)

wherein

5 X is

-C(O)-, -C(S)-, -C=NOH, or -CH(R⁷)- wherein R⁷ is hydrogen, hydroxy, C₁₋₇alkoxy or -NR⁸R⁹ (wherein R⁸ is a group -Y¹R¹⁰ (wherein Y¹ is a direct bond, -C(O)-, -C(S)-, -S-, -C(O)O-, -C(O)NR¹¹-, -SO₂- or -SO₂NR¹²- (wherein R¹¹ and R¹², which may be the same or different, each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁰ is selected

10 from one of the following four groups:

1) hydrogen, C₁₋₇alkyl or C₃₋₇cycloalkyl

(which alkyl or cycloalkyl group may bear one or more substituents selected from:

halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋

4alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, phenyl, nitro,

15 sulphate, phosphate and a group -Y²R¹³ (wherein Y² is -NR¹⁴C(O)- or -O-C(O)- (wherein R¹⁴ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹³ is C₁₋₇alkyl, C₃₋

7cycloalkyl or a group R¹⁵ wherein R¹⁵ is a phenyl group or a 5-10-membered aromatic

heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected

independently from O, N and S, which phenyl or aromatic heterocyclic group may bear

20 one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋

4haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋

4hydroxyalkoxy, carboxy, cyano, -CONR¹⁶R¹⁷ and -NR¹⁸COR¹⁹ (wherein R¹⁶, R¹⁷, R¹⁸ and R¹⁹, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋

3alkoxyC₂₋₃alkyl));

25 2) R¹⁵ wherein R¹⁵ is as defined hereinbefore;

3) C₂₋₇alkenylR¹⁵ (wherein R¹⁵ is as defined hereinbefore); and

4) C_{3-7} alkynyl R^{15} (wherein R^{15} is as defined hereinbefore));

and R^9 is hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl, which alkyl or cycloalkyl group may bear one or more substituents selected from C_{1-4} alkoxy and phenyl);

5 R^1 , R^2 and R^3 are each independently

hydrogen, PO_3H_2 , sulphate, C_{3-7} cycloalkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{1-7} alkanoyl, a group $R^{20}C_{1-7}$ alkyl (wherein R^{20} is phenyl which may bear one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} aminoalkyl and C_{1-4} hydroxyalkoxy), C_{1-7} alkyl or C_{1-7} alkylsulphonyl (which alkyl or alkylsulphonyl group may bear one or more substituents selected from:

- 10 halogeno, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^2R^{21}$ (wherein Y^2 is $-NR^{22}C(O)-$ or $-O-C(O)-$ (wherein R^{22} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{21} is C_{1-7} alkyl, C_{3-7} cycloalkyl or a group R^{23} wherein R^{23} is a phenyl group or a 5-10-membered
- 15 aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-CONR^{24}R^{25}$ and $-NR^{26}COR^{27}$ (wherein R^{24} , R^{25} , R^{26} and
- 20 R^{27} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl))));

with the proviso that at least two of R^1 , R^2 and R^3 are C_{1-7} alkyl;

R^4 , R^5 and R^6 are each independently selected from:

- 25 hydrogen, $-OPO_3H_2$, cyano, halogeno, nitro, amino, carboxy, hydroxy, C_{1-7} alkoxy, C_{1-7} alkanoyl, C_{1-7} thioalkoxy, C_{1-7} alkyl,
- (which alkyl group may bear one or more substituents selected from:
- halogeno, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy,
- 30 phenyl, sulphate, phosphate and a group $-Y^3R^{28}$ (wherein Y^3 is $-NR^{29}C(O)-$ or $-O-C(O)-$ (wherein R^{29} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{28} is C_{1-7} alkyl, C_{3-7} cycloalkyl or a group R^{30} wherein R^{30} is a phenyl group or a 5-10-membered aromatic

heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋

5 ₄hydroxyalkoxy, carboxy, cyano, -CONR³¹R³² and -NR³¹COR³² (wherein R³¹, R³², R³³ and R³⁴, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl))), and

a group -Y⁴R³⁵

(wherein Y⁴ is -C(O)-, -OC(O)-, -O-, -SO-, -SO₂-, -OSO₂-, -NR³⁶-, -NR³⁷C(O)-, -OC(O)O-,
10 ₋C(O)NR³⁸- or -NR³⁹C(O)O- (wherein R³⁶, R³⁷, R³⁸ and R³⁹, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and

R³⁵ is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, C₁₋₇alkyl, C₁₋₇alkoxy, C₁₋₇alkanoyl, aminoC₁₋₇alkylamino, C₁₋₇alkylaminoC₁₋₇alkylamino, di(C₁₋₇alkyl)aminoC₁₋₇alkylamino, C₁₋₇alkylphosphate

15 (which alkyl, alkoxy, alkanoyl, aminoalkylamino, alkylaminoalkylamino, dialkylaminoalkylamino, or alkylphosphate may bear one or more substituents selected from:

halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy,
20 phenyl, nitro, sulphate, phosphate and a group -Y⁵R⁴⁰ (wherein Y⁵ is -NR⁴¹C(O)-, -C(O)NR⁴²-, -C(O)-O- or -O-C(O)- (wherein R⁴¹ and R⁴² which may be the same or different each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R⁴⁰ is C₁₋

₇alkyl, C₃₋₇cycloalkyl, carboxyC₁₋₇alkyl or a group R⁴³ wherein R⁴³ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or
25 nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR⁴⁴R⁴⁵ and -NR⁴⁶COR⁴⁷ (wherein R⁴⁴, R⁴⁵, R⁴⁶ and R⁴⁷, which may be the same or
30 different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl))),

R⁴⁸ (wherein R⁴⁸ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected

independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from

- hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, phenyl, cyano, -
- 5 CONR⁴⁹R⁵⁰ and -NR⁵¹COR⁵² (wherein R⁴⁹, R⁵⁰, R⁵¹ and R⁵², which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl)), or
- R⁵³ (wherein R⁵³ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

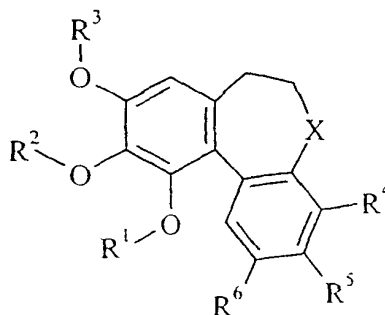
- 10 oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl and R⁵⁴ (wherein R⁵⁴ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl and C₁₋₄alkylsulphonylC₁₋₄alkyl))));
- 15

with the proviso that R⁵ is not hydroxy, alkoxy, substituted alkoxy, -OPO₃H₂, -O-C₁₋₇alkanoyl or benzyloxy;

and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof for example esters, amides and sulphides, in the manufacture of a

- 20 medicament for use in the production of a vascular damaging effect in warm-blooded animals such as humans.

According to another aspect of the present invention there is provided a compound of the formula IIa:



(IIa)

wherein

X is

-C(O)-, -C(S)-, -C=NOH, or -CH(R⁷)- wherein R⁷ is hydrogen, hydroxy, C₁₋₇alkoxy, -OR⁸ or -NR⁸R⁹ (wherein R⁸ is a group -Y¹R¹⁰ (wherein Y¹ is a direct bond, -C(O)-, -C(S)-, -S-, -

- 5 C(O)O-, -C(O)NR¹¹-, -SO₂- or -SO₂NR¹²- (wherein R¹¹ and R¹², which may be the same or different, each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁰ is selected from one of the following nine groups:

1) hydrogen, C₁₋₇alkyl, C₃₋₇cycloalkyl, C₁₋₄alkylY⁸C₁₋₄alkyl wherein Y⁸ is as defined hereinafter, or phenyl,

- 10 (which alkyl, cycloalkyl, alkylY⁸alkyl or phenyl group may bear one or more substituents selected from:

halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, carboxy, carbamoyl, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, phenyl, nitro, sulphate, phosphate,

- 15 Z¹ (wherein Z¹ represents a 5-6 membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄aminoalkyl, C₁₋₇alkanoyl, cyanoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl and Z² (wherein Z² is a 5-6-membered saturated

- 20 heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄aminoalkyl, C₁₋₇alkanoyl, cyanoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl and C₁₋₄alkylsulphonylC₁₋₄alkyl)),

- 25 C₁₋₄alkylZ¹ (wherein Z¹ is as defined hereinbefore), and

a group -Y²R¹³ (wherein Y² is -NR¹⁴C(O)- or -O-C(O)- (wherein R¹⁴ represents

hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹³ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a

- 30 group R¹⁵ wherein R¹⁵ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more

substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR¹⁶R¹⁷ and -NR¹⁸COR¹⁹ (wherein R¹⁶, R¹⁷, R¹⁸ and R¹⁹, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl));

5 ₃alkyl))));

2) R¹⁵ wherein R¹⁵ is as defined hereinbefore;

3) C₂₋₇alkenylR¹⁵ (wherein R¹⁵ is as defined hereinbefore);

4) C₃₋₇alkynylR¹⁵ (wherein R¹⁵ is as defined hereinbefore));

5) Z¹ (wherein Z¹ is as defined hereinbefore);

10 6) C₁₋₇alkylZ¹ (wherein Z¹ is as defined hereinbefore);

7) C₁₋₇alkylY⁸Z¹ (wherein Z¹ is as defined hereinbefore and Y⁸ is -C(O)-, -NR⁵⁹C(O)-, -NR⁵⁹C(O)C₁₋₄alkyl-, -C(O)NR⁶⁰- or -C(O)NR⁶⁰C₁₋₄alkyl-, (wherein R⁵⁹ and R⁶⁰, which may be the same or different, each represents hydrogen, C₁₋₃alkyl, C₁₋₃hydroxyalkyl or C₁₋₃alkoxyC₂₋₃alkyl));

15 8) (C₁₋₇alkyl)_cY⁹Z³ (wherein c is 0 or 1, Z³ is an amino acid group and Y⁹ is a direct bond, -C(O)- or -NR⁶¹- (wherein R⁶¹ is hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl)); and

9) C₁₋₇alkylR¹⁵ (wherein R¹⁵ is as defined hereinbefore);

and R⁹ is hydrogen, C₁₋₇alkyl or C₃₋₇cycloalkyl, which alkyl or cycloalkyl group may bear one or more substituents selected from C₁₋₄alkoxy and phenyl);

20 R¹, R² and R³ are each independently

hydrogen, PO₃H₂, sulphate, C₃₋₇cycloalkyl, C₂₋₇alkenyl, C₂₋₇alkynyl, C₁₋₇alkanoyl, a group R²⁰C₁₋₇alkyl (wherein R²⁰ is phenyl which may bear one or more substituents selected from C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄aminoalkyl and C₁₋₄hydroxyalkoxy), C₁₋₇alkyl or C₁₋₇alkylsulphonyl (which alkyl or alkylsulphonyl group may bear one or more substituents selected from:

25 halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -Y²R²¹ (wherein Y² is -NR²²C(O)- or -O-C(O)- (wherein R²² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²¹ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a group R²³ wherein R²³ is a phenyl group or a 5-10-membered
30 aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋

₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR²⁴R²⁵ and -NR²⁶COR²⁷ (wherein R²⁴, R²⁵, R²⁶ and R²⁷, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl));

5 with the proviso that at least two of R¹, R² and R³ are C₁₋₇alkyl;

R⁴ is

hydrogen, cyano, halogeno, nitro, amino, hydroxy, C₁₋₇alkoxy, C₁₋₇thioalkoxy, C₁₋₇alkanoyl or C₁₋₇alkyl,

(which alkyl group may bear one or more substituents selected from:

- 10 halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -Y³R²⁸ (wherein Y³ is -NR²⁹C(O)- or -O-C(O)- (wherein R²⁹ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁸ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a group R³⁰ wherein R³⁰ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR³¹R³² and -NR³¹COR³² (wherein R³¹, R³², R³³ and R³⁴, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- 15
- 20

R⁵ and R⁶ are each independently selected from

hydrogen, -OPO₃H₂, phosphonate, cyano; halogeno, nitro, amino, carboxy, carbamoyl, hydroxy, C₁₋₇alkoxy, C₁₋₇alkanoyl, C₁₋₇thioalkoxy, C₁₋₇alkyl,

- 25 (which alkyl group may bear one or more substituents selected from: halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, sulphate, phosphate and a group -Y³R²⁸ (wherein Y³ is -NR²⁹C(O)- or -O-C(O)- (wherein R²⁹ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁸ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a group R³⁰ wherein R³⁰ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear
- 30

one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR³¹R³² and -NR³¹COR³² (wherein R³¹, R³², R³³ and R³⁴, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl))), and

5 a group -Y⁴R³⁵

(wherein Y⁴ is -C(O)-, -OC(O)-, -O-, -SO-, -SO₂-, -OSO₂-, -NR³⁶-, -C₁₋₄alkylNR³⁶-, -C₁₋₄alkylC(O)-, -NR³⁷C(O)-, -OC(O)O-, -C(O)NR³⁸- or -NR³⁹C(O)O- (wherein R³⁶, R³⁷, R³⁸ and R³⁹, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and

10 R³⁵ is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, hydroxy, amino, C₁₋₇alkyl, C₁₋₇alkoxy, C₁₋₇alkanoyl, C₁₋₇alkylamino, di(C₁₋₇alkyl)amino, aminoC₁₋₇alkylamino, C₁₋₇alkylaminoC₁₋₇alkylamino, C₁₋₇alkanoylaminoC₁₋₇alkyl, di(C₁₋₇alkyl)aminoC₁₋₇alkylamino, C₁₋₇alkylphosphate, C₁₋₇alkylphosphonate, C₁₋₇alkylcarbamoylC₁₋₇alkyl,

15 (which alkyl, alkoxy, alkanoyl, alkylamino, dialkylamino, aminoalkylamino, alkylaminoalkylamino, alkanoylaminoalkyl, dialkylaminoalkylamino, alkylphosphate, alkylphosphonate or alkylcarbamoylalkyl, may bear one or more substituents selected from:

20 halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -Y⁵R⁴⁰ (wherein Y⁵ is -NR⁴¹C(O)-, -C(O)NR⁴²-, -C(O)-O- or -O-C(O)- (wherein R⁴¹ and R⁴² which may be the same or different each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and

25 R⁴⁰ is C₁₋₇alkyl, C₃₋₇cycloalkyl, carboxyC₁₋₇alkyl or a group R⁴³ wherein R⁴³ is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR⁴⁴R⁴⁵ and -NR⁴⁶COR⁴⁷ (wherein R⁴⁴, R⁴⁵, R⁴⁶ and R⁴⁷, which

30

may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl))),

R^{48} (wherein R^{48} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected

5 independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from

hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino C_{1-4} alkyl, di(C_{1-4} hydroxyalkyl)amino C_{1-4} alkyl, di(C_{1-4} aminoalkyl)amino C_{1-4} alkyl, C_{1-4} hydroxyalkoxy, 10 carboxy, C_{1-4} carboxyalkyl, phenyl, cyano, $-CONR^{49}R^{50}$, $-NR^{51}COR^{52}$ (wherein R^{49} , R^{50} , R^{51} and R^{52} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and C_{1-4} alkyl R^{53} (wherein R^{53} is as defined hereinafter),

C_{1-7} alkyl R^{48} (wherein R^{48} is as defined hereinbefore),

R^{53} (wherein R^{53} is a 5-6-membered saturated heterocyclic group (linked via carbon or 15 nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which

heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} carboxyalkyl, C_{1-4} aminoalkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} alkylsulphonyl C_{1-4} alkyl and R^{54} (wherein R^{54} is a 5-6-membered saturated heterocyclic group (linked via 20 carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl and C_{1-4} alkylsulphonyl C_{1-4} alkyl)), or

$(CH_2)_aY^6(CH_2)_bR^{53}$ (wherein R^{53} is as defined hereinbefore, a is 0, or an integer 1-4, b is 0 25 or an integer 1-4 and Y^6 represents a direct bond, $-O-$, $-C(O)-$, $-NR^{55}-$, $-NR^{56}C(O)-$ or $-C(O)NR^{57}-$ (wherein R^{55} , R^{56} , and R^{57} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl), and wherein one or more of the $(CH_2)_a$ or $(CH_2)_b$ groups may bear one or more substituents selected from hydroxy, amino and halogeno));

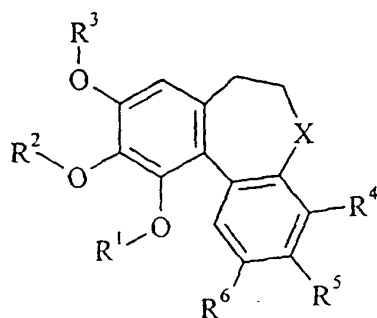
30 with the proviso that R^5 is not hydroxy, alkoxy, substituted alkoxy (wherein R^5 is Y^4R^{35} and Y^4 is $-O-$ and R^{35} is C_{1-7} alkyl bearing one or more substituents selected from the list given hereinbefore), $-OPO_3H_2$, $-O-C_{1-7}$ alkanoyl or benzyloxy;

with the further proviso that at least one of R^5 or R^6 is a group $-Y^4R^{35}$ (wherein Y^4 and R^{35} are as defined hereinbefore) but with the further provisos

that when R^5 is $-Y^4R^{35}$ and R^6 is hydrogen, hydroxy, methoxy or methoxycarbonyl, $-Y^4R^{35}$ is not selected from cases wherein:

- 5 Y^4 is $-C(O)-$, $-OC(O)-$, $-O-$, $-SO-$, $-OSO_2-$, $-NR^{36}-$, $-NR^{37}C(O)-$ or $-C(O)NR^{38}-$ (wherein R^{36} , R^{37} and R^{38} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{35} is a glycine, valine or lysine group, a dipeptide of glycine and valine groups, C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkanoyl,
- 10 (which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno, hydroxy, and a group $-Y^5R^{40}$ (wherein Y^5 is $-O-C(O)-$ and R^{40} is C_{1-7} alkyl)), or R^{48} (wherein R^{48} is a tetrazolyl group (which may or may not be substituted as hereinbefore defined), a phenyl group or a benzyl group which phenyl or benzyl group may bear one or more substituents selected from C_{1-4} alkyl); and
- 15 that when R^6 is $-Y^4R^{35}$ and R^5 is hydrogen, hydroxy, methoxy or methoxycarbonyl, $-Y^4R^{35}$ is not selected from cases wherein: Y^4 is $-C(O)-$, $-O-$ or $-OSO_2-$ and R^{35} is C_{1-7} alkyl, C_{1-7} alkoxy
- 20 (which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno), R^{48} (wherein R^{48} is a benzyl group which benzyl group may bear one or more substituents selected from C_{1-4} alkyl), or R^{53} (wherein R^{53} is piperidinyl);
- 25 and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof.

According to a further aspect of the present invention there is provided a compound of the formula IIa:



(IIa)

wherein

X is

- 5 -C(O)-, -C(S)-, -C=NOH, or -CH(R⁷)- wherein R⁷ is hydrogen, hydroxy, C₁₋₇alkoxy, -OR⁸ or -NR⁸R⁹ (wherein R⁸ is a group -Y¹R¹⁰ (wherein Y¹ is a direct bond, -C(O)-, -C(S)-, -S-, -C(O)O-, -C(O)NR¹¹-, -SO₂- or -SO₂NR¹²- (wherein R¹¹ and R¹², which may be the same or different, each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁰ is selected from one of the following nine groups:

- 10 1) hydrogen, C₁₋₇alkyl, C₃₋₇cycloalkyl, C₁₋₄alkylY⁸C₁₋₄alkyl wherein Y⁸ is as defined hereinafter, or phenyl,

(which alkyl, cycloalkyl, alkylY⁸alkyl or phenyl group may bear one or more substituents selected from:

- 15 halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, carboxy, carbamoyl, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, phenyl, nitro, sulphate, phosphate,

Z¹ (wherein Z¹ represents a 5-6 membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

- 20 oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄aminoalkyl, C₁₋₇alkanoyl, cyanoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl and Z² (wherein Z² is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1
- 25 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} aminoalkyl, C_{1-7} alkanoyl, cyano C_{1-4} alkyl, C_{1-4} alkoxy C_{1-4} alkyl and C_{1-4} alkylsulphonyl(C_{1-4} alkyl)),

C_{1-4} alkyl Z^1 (wherein Z^1 is as defined hereinbefore), and

- 5 a group $-Y^2R^{13}$ (wherein Y^2 is $-NR^{14}C(O)-$ or $-O-C(O)-$ (wherein R^{14} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{13} is C_{1-7} alkyl, C_{3-7} cycloalkyl or a group R^{15} wherein R^{15} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more
- 10 substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-CONR^{16}R^{17}$ and $-NR^{18}COR^{19}$ (wherein R^{16} , R^{17} , R^{18} and R^{19} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));
- 15 2) R^{15} wherein R^{15} is as defined hereinbefore;
- 3) C_{2-7} alkenyl R^{15} (wherein R^{15} is as defined hereinbefore);
- 4) C_{3-7} alkynyl R^{15} (wherein R^{15} is as defined hereinbefore));
- 5) Z^1 (wherein Z^1 is as defined hereinbefore);
- 6) C_{1-7} alkyl Z^1 (wherein Z^1 is as defined hereinbefore);
- 20 7) C_{1-7} alkyl Y^8Z^1 (wherein Z^1 is as defined hereinbefore and Y^8 is $-C(O)-$, $-NR^{59}C(O)-$, $-NR^{59}C(O)C_{1-4}$ alkyl-, $-C(O)NR^{60}-$ or $-C(O)NR^{60}C_{1-4}$ alkyl-, (wherein R^{59} and R^{60} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl, C_{1-3} hydroxyalkyl or C_{1-3} alkoxy C_{2-3} alkyl));
- 8) $(C_{1-7}alkyl)_cY^9Z^3$ (wherein c is 0 or 1, Z^3 is an amino acid group and Y^9 is a direct bond, $-C(O)-$ or $-NR^{61}-$ (wherein R^{61} is hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl)); and
- 25 9) $C_{1-7}alkylR^{15}$ (wherein R^{15} is as defined hereinbefore);
- and R^9 is hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl, which alkyl or cycloalkyl group may bear one or more substituents selected from C_{1-4} alkoxy and phenyl);
- R^1 , R^2 and R^3 are each independently
- 30 hydrogen, PO_3H_2 , sulphate, C_{3-7} cycloalkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{1-7} alkanoyl, a group $R^{20}C_{1-7}alkyl$ (wherein R^{20} is phenyl which may bear one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} aminoalkyl and C_{1-4} hydroxyalkoxy), C_{1-7} alkyl or C_{1-7} alkylsulphonyl

(which alkyl or alkylsulphonyl group may bear one or more substituents selected from: halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -Y²R²¹ (wherein Y² is -NR²²C(O)- or -O-C(O)- (wherein R²² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²¹ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a group R²³ wherein R²³ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR²⁴R²⁵ and -NR²⁶COR²⁷ (wherein R²⁴, R²⁵, R²⁶ and R²⁷, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl))));

with the proviso that at least two of R¹, R² and R³ are C₁₋₇alkyl;

15 R⁴ is hydrogen, cyano, halogeno, nitro, amino, hydroxy, C₁₋₇alkoxy, C₁₋₇thioalkoxy, C₁₋₇alkanoyl or C₁₋₇alkyl,

(which alkyl group may bear one or more substituents selected from: halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -Y³R²⁸ (wherein Y³ is -NR²⁹C(O)- or -O-C(O)- (wherein R²⁹ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁸ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a group R³⁰ wherein R³⁰ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR³¹R³² and -NR³¹COR³² (wherein R³¹, R³², R³³ and R³⁴, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl))));

R⁵ and R⁶ are each independently selected from

hydrogen, $-OPO_3H_2$, phosphonate, cyano, halogeno, nitro, amino, carboxy, carbamoyl, hydroxy, C_{1-7} alkoxy, C_{1-7} alkanoyl, C_{1-7} thioalkoxy, C_{1-7} alkyl,

(which alkyl group may bear one or more substituents selected from:

halogeno, amino, C_{1-4} alkylamino, $di(C_{1-4}alkyl)amino$, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy,

- 5 phenyl, sulphate, phosphate and a group $-Y^3R^{28}$ (wherein Y^3 is $-NR^{29}C(O)-$ or $-O-C(O)-$ (wherein R^{29} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{28} is C_{1-7} alkyl, C_{3-7} cycloalkyl or a group R^{30} wherein R^{30} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected
- 10 independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-CONR^{31}R^{32}$ and $-NR^{31}COR^{32}$ (wherein R^{31} , R^{32} , R^{33} and R^{34} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl))), and
- 15 a group $-Y^4R^{35}$

(wherein Y^4 is $-C(O)-$, $-OC(O)-$, $-O-$, $-SO-$, $-SO_2-$, $-OSO_2-$, $-NR^{36}-$, $-C_{1-4}alkylNR^{36}-$, $-C_{1-4}alkylC(O)-$, $-NR^{37}C(O)-$, $-OC(O)O-$, $-C(O)NR^{38}-$ or $-NR^{39}C(O)O-$ (wherein R^{36} , R^{37} , R^{38} and R^{39} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and

- 20 R^{35} is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, hydroxy, amino, C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkanoyl, C_{1-7} alkylamino, $di(C_{1-7}alkyl)amino$, $aminoC_{1-7}alkylamino$, $C_{1-7}alkylaminoC_{1-7}alkylamino$, $C_{1-7}alkanoylaminoC_{1-7}alkyl$, $di(C_{1-7}alkyl)aminoC_{1-7}alkylamino$, $C_{1-7}alkylphosphate$, $C_{1-7}alkylphosphonate$, $C_{1-7}alkylcarbamoylC_{1-7}alkyl$,
- 25

(which alkyl, alkoxy, alkanoyl, alkylamino, dialkylamino, aminoalkylamino, alkylaminoalkylamino, alkanoylaminoalkyl, dialkylaminoalkylamino, alkylphosphate, alkylphosphonate or alkylcarbamoylalkyl, may bear one or more substituents selected from:

- 30 halogeno, amino, C_{1-4} alkylamino, $di(C_{1-4}alkyl)amino$, hydroxy, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^5R^{40}$ (wherein Y^5

is $-NR^{41}C(O)-$, $-C(O)NR^{42}-$, $-C(O)-O-$ or $-O-C(O)-$ (wherein R^{41} and R^{42} which may be the same or different each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{40} is C_{1-7} alkyl, C_{3-7} cycloalkyl, carboxy C_{1-7} alkyl or a group R^{43} wherein R^{43} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-CONR^{44}R^{45}$ and $-NR^{46}COR^{47}$ (wherein R^{44} , R^{45} , R^{46} and R^{47} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl))),

R^{48} (wherein R^{48} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from

hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino C_{1-4} alkyl, di(C_{1-4} hydroxyalkyl)amino C_{1-4} alkyl, di(C_{1-4} aminoalkyl)amino C_{1-4} alkyl, C_{1-4} hydroxyalkoxy, carboxy, C_{1-4} carboxyalkyl, phenyl, cyano, $-CONR^{49}R^{50}$, $-NR^{51}COR^{52}$ (wherein R^{49} , R^{50} , R^{51} and R^{52} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and C_{1-4} alkyl R^{53} (wherein R^{53} is as defined hereinafter),

C_{1-7} alkyl R^{48} (wherein R^{48} is as defined hereinbefore),

R^{53} (wherein R^{53} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} carboxyalkyl, C_{1-4} aminoalkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} alkylsulphonyl C_{1-4} alkyl and R^{54} (wherein R^{54} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl and C_{1-4} alkylsulphonyl(C_{1-4} alkyl)), or

(CH₂)_aY⁶(CH₂)_bR⁵³ (wherein R⁵³ is as defined hereinbefore, a is 0, or an integer 1-4, b is 0 or an integer 1-4 and Y⁶ represents a direct bond, -O-, -C(O)-, -NR⁵⁵-, -NR⁵⁶C(O)- or -C(O)NR⁵⁷- (wherein R⁵⁵, R⁵⁶, and R⁵⁷, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), and wherein one or more of the (CH₂)_a or (CH₂)_b groups may bear one or more substituents selected from hydroxy, amino and halogeno));

with the proviso that R⁵ is not hydroxy, alkoxy, substituted alkoxy (wherein R⁵ is Y⁴R³⁵ and Y⁴ is -O- and R³⁵ is C₁₋₇alkyl bearing one or more substituents selected from the list given hereinbefore), -OPO₃H₂, -O-C₁₋₇alkanoyl or benzyloxy;

10 with the further proviso that at least one of R⁵ or R⁶ is a group -Y⁴R³⁵ (wherein Y⁴ and R³⁵ are as defined hereinbefore) but with the further provisos

that when R⁵ is -Y⁴R³⁵ and R⁶ is hydrogen, hydroxy, methoxy or methoxycarbonyl, -Y⁴R³⁵ is not selected from cases wherein:

15 Y⁴ is -C(O)-, -OC(O)-, -O-, -SO-, -OSO₂-, -NR³⁶-, -NR³⁷C(O)- or -C(O)NR³⁸- (wherein R³⁶, R³⁷ and R³⁸, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁵ is a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, C₁₋₇alkyl, C₁₋₇alkoxy, C₁₋₇alkanoyl,

20 (which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno, hydroxy, and a group -Y³R⁴⁰ (wherein Y³ is -O-C(O)- and R⁴⁰ is C₁₋₇alkyl)), or

R⁴⁸ (wherein R⁴⁸ is a tetrazolyl group (which may or may not be substituted as hereinbefore defined), a phenyl group or a benzyl group which phenyl or benzyl group may bear one or more substituents selected from C₁₋₄alkyl); and

25 that when R⁶ is -Y⁴R³⁵ and R⁵ is hydrogen, hydroxy, methoxy or methoxycarbonyl, -Y⁴R³⁵ is not selected from cases wherein:

Y⁴ is -C(O)-, -O- or -OSO₂- and R³⁵ is C₁₋₇alkyl, C₁₋₇alkoxy

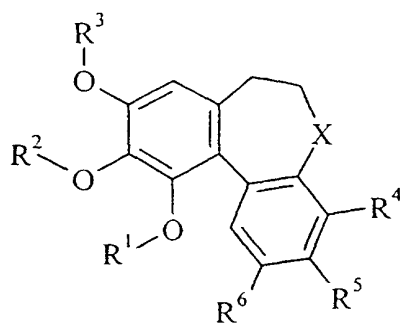
30 (which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno),

R⁴⁸ (wherein R⁴⁸ is a benzyl group which benzyl group may bear one or more substituents selected from C₁₋₄alkyl), or

R^{53} (wherein R^{53} is piperidiny);
and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof.

According to a further aspect of the present invention there is provided the use of a
5 compound of the formula IIa as defined hereinbefore, and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof, in the manufacture of a medicament for use in the production of a vascular damaging effect in warm-blooded animals such as humans.

According to another aspect of the present invention there is provided the use of a
10 compound of the formula IIb:



(IIb)

wherein

15 X is

-C(O)-, -C(S)-, or -CH(R⁷)- wherein R⁷ is hydrogen, hydroxy or -NR⁸R⁹ (wherein R⁸ is a group -Y¹R¹⁰ (wherein Y¹ is a direct bond, -C(O)-, -C(S)-, -C(O)O-, -C(O)NR¹¹-, -SO₂- or -SO₂NR¹²- (wherein R¹¹ and R¹², which may be the same or different, each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁰ is selected from one of the

20 following two groups:

1) hydrogen, C₁₋₇alkyl or C₃₋₇cycloalkyl

(which alkyl or cycloalkyl group may bear one or more substituents selected from:

halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋

4alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, phenyl, nitro,

25 sulphate, phosphate and a group -Y²R¹³ (wherein Y² is -NR¹⁴C(O)- or -O-C(O)- (wherein R¹⁴ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹³ is C₁₋₇alkyl, C₃₋

7cycloalkyl or a group R¹⁵ wherein R¹⁵ is a phenyl group or a 5-10-membered aromatic

- heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR¹⁶R¹⁷ and -NR¹⁸COR¹⁹ (wherein R¹⁶, R¹⁷, R¹⁸ and R¹⁹, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl)); and
- 2) R¹⁵ wherein R¹⁵ is as defined hereinbefore;
- and R⁹ is hydrogen, C₁₋₇alkyl or C₃₋₇cycloalkyl, which alkyl or cycloalkyl group may bear one or more substituents selected from C₁₋₄alkoxy and phenyl);
- R¹, R² and R³ are each independently hydrogen, PO₃H₂, sulphate, C₃₋₇cycloalkyl, C₂₋₇alkenyl, C₂₋₇alkynyl, C₁₋₇alkanoyl, a group R²⁰C₁₋₇alkyl (wherein R²⁰ is phenyl which may bear one or more substituents selected from C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄aminoalkyl and C₁₋₄hydroxyalkoxy), C₁₋₇alkyl or C₁₋₇alkylsulphonyl (which alkyl or alkylsulphonyl group may bear one or more substituents selected from: halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -Y²R²¹ (wherein Y² is -NR²²C(O)- or -O-C(O)- (wherein R²² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²¹ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a group R²³ wherein R²³ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR²⁴R²⁵ and -NR²⁶COR²⁷ (wherein R²⁴, R²⁵, R²⁶ and R²⁷, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- with the proviso that at least two of R¹, R² and R³ are C₁₋₇alkyl;
- R⁴ is
- hydrogen, cyano, halogeno, nitro, amino, hydroxy, C₁₋₇alkoxy, C₁₋₇thioalkoxy, C₁₋₇alkanoyl or C₁₋₇alkyl,
- (which alkyl group may bear one or more substituents selected from:

halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -Y³R²⁸ (wherein Y³ is -NR²⁹C(O)- or -O-C(O)- (wherein R²⁹ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁸ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a group R³⁰ wherein R³⁰ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR³¹R³² and -NR³¹COR³² (wherein R³¹, R³², R³³ and R³⁴, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl))));

R⁵ and R⁶ are each independently selected from

hydrogen, -OPO₃H₂, cyano, halogeno, nitro, amino, carboxy, hydroxy, C₁₋₇alkoxy, C₁₋₇alkanoyl, C₁₋₇thioalkoxy, C₁₋₇alkyl,

(which alkyl group may bear one or more substituents selected from:

halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, sulphate, phosphate and a group -Y³R²⁸ (wherein Y³ is -NR²⁹C(O)- or -O-C(O)- (wherein R²⁹ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁸ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a group R³⁰ wherein R³⁰ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR³¹R³² and -NR³¹COR³² (wherein R³¹, R³², R³³ and R³⁴, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl))), and

a group -Y⁴R³⁵

(wherein Y⁴ is -C(O)-, -OC(O)-, -O-, -SO-, -SO₂-, -OSO₂-, -NR³⁶-, -NR³⁷C(O)-, -OC(O)O-, -C(O)NR³⁸- or -NR³⁹C(O)O- (wherein R³⁶, R³⁷, R³⁸ and R³⁹, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁵ is

a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkanoyl, amino C_{1-7} alkylamino, C_{1-7} alkylamino C_{1-7} alkylamino, di(C_{1-7} alkyl)amino C_{1-7} alkylamino, C_{1-7} alkylphosphate

(which alkyl, alkoxy, alkanoyl, aminoalkylamino, alkylaminoalkylamino,

5 dialkylaminoalkylamino, or alkylphosphate may bear one or more substituents selected from:

halogeno, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^5R^{40}$ (wherein Y^5 is $-NR^{41}C(O)-$, $-C(O)NR^{42}-$, $-C(O)-O-$ or $-O-C(O)-$ (wherein R^{41} and R^{42} which may be the same or
10 different each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{40} is C_{1-7} alkyl, C_{3-7} cycloalkyl, carboxy C_{1-7} alkyl or a group R^{43} wherein R^{43} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which
15 phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-CONR^{44}R^{45}$ and $-NR^{46}COR^{47}$ (wherein R^{44} , R^{45} , R^{46} and R^{47} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl))),

20 R^{48} (wherein R^{48} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, phenyl, cyano, $-CONR^{49}R^{50}$ and $-NR^{51}COR^{52}$ (wherein R^{49} , R^{50} , R^{51} and R^{52} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl)), or

25 R^{53} (wherein R^{53} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which
30 heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} alkylsulphonyl C_{1-4} alkyl and R^{54} (wherein R^{54} is a 5-6-membered saturated heterocyclic group (linked via carbon or

nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl and C_{1-4} alkylsulphonyl(C_{1-4} alkyl));

- 5 with the proviso that R^5 is not hydroxy, alkoxy, substituted alkoxy, $-OPO_3H_2$, $-O-C_{1-7}$ alkanoyl or benzyloxy;

with the further proviso that at least one of R^5 or R^6 is a group $-Y^4R^{35}$ (wherein Y^4 and R^{35} are as defined hereinbefore) but with the further provisos

that when R^5 is $-Y^4R^{35}$ and R^6 is hydrogen, hydroxy or methoxy $-Y^4R^{35}$ is not selected from

- 10 cases wherein:

Y^4 is $-C(O)-$, $-OC(O)-$, $-O-$, $-SO-$, $-OSO_2-$, $-NR^{36}-$, $-NR^{37}C(O)-$ or $-C(O)NR^{38}-$ (wherein R^{36} , R^{37} and R^{38} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{35} is

- 15 a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkanoyl,

(which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from:

halogeno, hydroxy, and a group $-Y^5R^{40}$ (wherein Y^5 is $-C(O)-O-$ or $-O-C(O)-$ and R^{40} is C_{1-7} alkyl)), or

- 20 R^{48} (wherein R^{48} is a phenyl group or a benzyl group which phenyl or benzyl group may bear one or more substituents selected from C_{1-7} alkyl); and

that when R^6 is $-Y^4R^{35}$ and R^5 is hydrogen, hydroxy or methoxy $-Y^4R^{35}$ is not selected from cases wherein:

Y^4 is $-C(O)-$, $-O-$ or $-OSO_2-$ and R^{35} is

C_{1-7} alkyl, C_{1-7} alkoxy

- 25 (which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno),

R^{48} (wherein R^{48} is a benzyl group which phenyl or benzyl group may bear one or more substituents selected from C_{1-7} alkyl), or

R^{53} (wherein R^{53} is piperidinyl);

- 30 and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof for example esters, amides and sulphides, in the manufacture of a

medicament for use in the production of a vascular damaging effect in warm-blooded animals such as humans.

According to a further aspect of the present invention there is provided a compound of the formula IIb as defined hereinbefore, and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof for example esters, amides and sulphides.

Preferred compounds of the present invention include:

(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-
{[(2*R*)-2,6-diaminohexanoyl]amino} propanoate,

10 (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-[(2-aminoacetyl)amino]propanoate,

N-{[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]oxymethyl}-2-morpholinoacetamide,

(2*S*,3*S*,4*S*,5*R*,6*R*)-6-{[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-
15 dibenzo[*a,c*]cyclohepten-3-yl]oxy}-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-carboxylic acid,
N-[(5*S*)-3-(4-{4-methylpiperazin-1-ylmethyl}phenylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide,

N-[(5*S*)-3-(4-{morpholinomethyl}phenylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide,

20 (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-[4-methylpiperazin-1-ylcarbonyl]propanoate,

5-{[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]oxycarbonyl}pentanoic acid,

4-(3-{[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-
25 yl]oxy-3-oxopropyl}benzoic acid and

(2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]-2-amino-3-hydroxypropanamide,

and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof.

30 More preferred compounds of the present invention include:

(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-
{[(2*R*)-2,6-diaminohexanoyl]amino} propanoate,

(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-[(2-aminoacetyl)amino]propanoate,

N-[(5*S*)-3-(4-{4-methylpiperazin-1-ylmethyl}phenylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide,

5 *N*-[(5*S*)-3-(4-{morpholinomethyl}phenylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide,

(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-[4-methylpiperazin-1-ylcarbonyl]propanoate,

5-[{(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl}oxycarbonyl]pentanoic acid,

4-(3-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]oxy-3-oxopropyl)benzoic acid and

(2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]-2-amino-3-hydroxypropanamide,

15 and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof.

Especially preferred compounds of the present invention include:

N-[(5*S*)-3-(4-{4-methylpiperazin-1-ylmethyl}phenylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide and

20 (2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]-2-amino-3-hydroxypropanamide,

and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof.

In another embodiment of the present invention preferred compounds include (2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]-2-amino-5-[(2-nitroethanimidoyl)amino]pentanamide, and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof.

In one embodiment of the invention preferred compounds include those in which R¹, R² and R³ are each alkyl, Y⁴ is NH and R³⁵ is an acyl group derived from a natural alpha-amino acid such as glycine, L-alanine or L-serine.

In one embodiment of the invention more preferred compounds include compounds wherein R¹, R² and R³ are each methyl, R⁴ is hydrogen and X is -CH(NHC(O)CH₃)-.

In another embodiment of the invention particular compounds include compounds wherein R^1 , R^2 and R^3 are each alkyl and R^{35} is amino C_{1-7} alkylamino, C_{1-7} alkylamino C_{1-7} alkylamino, di(C_{1-7} alkyl)amino C_{1-7} alkylamino, 1-piperazinyl or 4-(piperidino)piperidin-1-yl.

In another embodiment of the invention further particular compounds include
5 compounds wherein R^1 , R^2 and R^3 are each alkyl, R^4 is hydrogen and X is $-\text{CH}(\text{NHC}(\text{O})\text{CH}_3)-$.

In another embodiment of the invention more particular compounds include compounds wherein R^1 , R^2 and R^3 are each alkyl and R^4 and R^6 are each hydrogen.

In another embodiment of the invention especially preferred compounds include compounds wherein R^1 , R^2 and R^3 are each methyl and R^{35} is a substituted acyl group.

10 Preferred compounds of the present invention include:

N-[3-(alanyl amino)-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-yl]acetamide and salts thereof, pharmaceutically acceptable salts thereof, solvates and hydrates thereof, and prodrugs thereof for example esters, amides and sulphides.

A preferred compound for use in the manufacture of a medicament for use in the production
15 of a vascular damaging effect in warm-blooded animals such as humans is *N*-[3-amino-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-5-yl]acetamide.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore', or 'hereinafter defined' or 'defined hereinafter', the said group encompasses the first occurring and broadest definition
20 as well as each and all of the preferred definitions for that group.

In this specification unless stated otherwise the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms. Unless otherwise stated the term "alkyl" advantageously refers to chains with 1-7
25 carbon atoms, preferably 1-4 carbon atoms. The term "alkoxy" as used herein, unless stated otherwise includes "alkyl"-O- groups in which "alkyl" is as hereinbefore defined. The term "aryl" as used herein unless stated otherwise includes reference to a C_{6-10} aryl group which may, if desired, carry one or more substituents selected from halogeno, alkyl, haloalkyl, alkoxy, hydroxy, amino, nitro and cyano, (wherein alkyl, haloalkyl and alkoxy are as
30 hereinbefore and hereinafter defined). The term "aryloxy" as used herein unless otherwise stated includes "aryl"-O-groups in which "aryl" is as hereinbefore defined. The term "sulphonyloxy" as used herein refers to alkylsulphonyloxy and arylsulphonyloxy groups in

which "alkyl" and "aryl" are as hereinbefore defined. The term "heteroaryl" as used herein unless stated otherwise includes reference to a C₆₋₁₀aryl group containing one or more ring heteroatoms selected from O, N and S which heteroaryl group may, if desired, carry one or more substituents selected from halogeno, alkyl, haloalkyl, alkoxy, hydroxy, amino, nitro and cyano, (wherein alkyl, haloalkyl and alkoxy are as hereinbefore and hereinafter defined). The term "alkanoyl" as used herein unless otherwise stated includes formyl and alkylC=O groups in which "alkyl" is as defined hereinbefore, for example C₂alkanoyl is ethanoyl and refers to CH₃C=O, C₁alkanoyl is formyl and refers to CHO. In this specification unless stated otherwise the term "alkenyl" includes both straight and branched chain alkenyl groups but references to individual alkenyl groups such as 2-butenyl are specific for the straight chain version only. Unless otherwise stated the term "alkenyl" advantageously refers to chains with 2-7 carbon atoms, preferably 2-4 carbon atoms. In this specification unless stated otherwise the term "alkynyl" includes both straight and branched chain alkynyl groups but references to individual alkynyl groups such as 2-butyne are specific for the straight chain version only. Unless otherwise stated the term "alkynyl" advantageously refers to chains with 2-7 carbon atoms, preferably 2-4 carbon atoms. The term "halogeno" means fluoro, chloro, bromo or iodo unless otherwise stated. A haloalkyl group is an alkyl group as defined hereinbefore substituted with one or more halogeno groups for example trifluoromethyl and dichloromethyl. A hydroxyalkyl group is an alkyl group as defined hereinbefore substituted with one or more hydroxy groups.

In this specification unless stated otherwise the term "acyl" refers to a group linked via a carbonyl group. "Acyl" includes a group -C(O)-R⁵⁸ wherein R⁵⁸ is an alkyl, aryl or heteroaryl group as hereinbefore defined, or -C(O)-R⁵⁸ is derived from an amino acid.

In this specification mono-peptide means an amino acid including α -amino acids β -amino acids and γ -amino acids. The amino acids may be L-isomers or D-isomers, preferably L-isomers. Preferred amino acids include glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, β -alanine and ornithine. More preferred amino acids include serine, threonine, arginine, glycine, alanine, β -alanine and lysine. Especially preferred amino acids include serine, threonine, arginine, alanine and β -alanine.

An aromatic heterocyclic group includes those selected from pyridyl, pyrimidyl, furyl, thienyl, pyrrolyl, pyrazolyl, indolyl, benzofuryl, benzothienyl, benzothiazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, quinolyl and isoquinolyl.

For the avoidance of any doubt, it is to be understood that when Y^1 is, for example, a group of formula $-C(O)NR^{11}-$, it is the nitrogen atom bearing the R^{11} group which is attached to the group R^{10} and the carbonyl group ($C(O)$) is attached to the nitrogen atom which is linked to the hepten ring. A similar convention applies to the other two atom Y^1 linking groups such as $-SO_2NR^{12}-$. An analogous convention applies to other groups. It is further to be understood that when Y^1 represents $-C(O)NR^{11}-$ and R^{11} is C_{1-3} alkoxy C_{2-3} alkyl it is the C_{2-3} alkyl moiety which is linked to the nitrogen atom of Y^1 and an analogous convention applies to other groups.

For the avoidance of any doubt it is to be understood that when Y^2 is, for example, a group of formula $-OC(O)-$ it is the oxygen atom which is bound to the substituted group and the carbonyl group ($C(O)$) which is bound to R^{13} and an analogous convention applies to other groups.

For the avoidance of any doubt it is to be understood that when Y^4 is, for example, a group of formula $-NR^{39}C(O)O-$ it is the nitrogen atom which is bound to the benz ring and the oxygen atom which is bound to R^{35} and an analogous convention applies to other groups.

For the avoidance of any doubt it is to be understood that when R^{35} is a group C_{1-4} alkyl R^{48} it is the alkyl chain which is linked to Y^4 , similarly when R^{35} is a group $(CH_2)_aY^6(CH_2)_bR^{53}$ it is the $(CH_2)_a$ group which is linked to Y^4 and a similar convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when a group carries a C_{1-4} alkylamino substituent it is the amino moiety which is attached to the group whereas when a group carries a C_{1-4} aminoalkyl substituent it is the C_{1-4} alkyl moiety which is attached to the group and an analogous convention applies to other substituents.

Within the present invention it is to be understood that a compound of the formula I or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has vascular damaging activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of

the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It will be appreciated that compounds of the formula I or a salt thereof may possess an asymmetric carbon atom. Such an asymmetric carbon atom is also involved in the tautomerism described above, and it is to be understood that the present invention encompasses any chiral form (including both pure enantiomers and racemic mixtures), as well as any tautomeric form, which has vascular damaging activity, and is not to be limited merely to any one tautomeric form or chiral form utilised within the formulae drawings. It is to be understood that the invention encompasses all optical and diastereomers which have vascular damaging activity.

It is also to be understood that certain compounds of the formula I and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have vascular damaging activity.

The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula I as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. Suitable salts include hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates. In addition where the compounds of formula I are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for

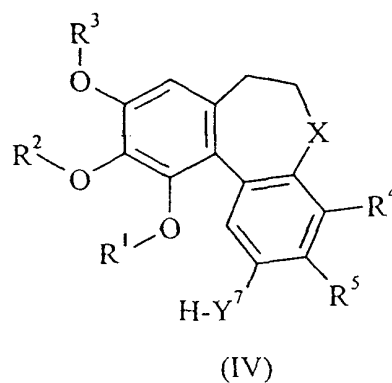
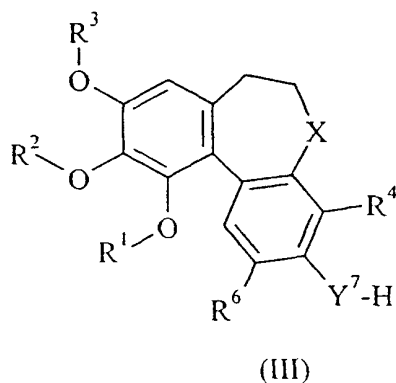
example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Compounds of Formula I may be prepared by any process known to a person skilled in the art. Such processes include, for example, solid phase synthesis. Compounds of Formula I may be prepared by a number of processes as generally described hereinbelow and more specifically in the Examples hereinafter. In the general preparations described hereinafter it may be necessary to employ protecting groups which are then removed during the final stages of the synthesis. The appropriate use of such protecting groups and processes for their removal will be readily apparent to those skilled in the art. Processes for the preparation of novel compounds of formula I, are provided as a further feature of the invention and are as described hereinafter. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Thus, the following processes (a) to (i) and (i) to (iii) constitute further features of the present invention.

Synthesis of Compounds of Formula I

(a) Thus according to a further aspect of the invention a compound of formula I, in which R^5 or R^6 is a group Y^4R^{35} (wherein R^{35} is as defined hereinbefore and Y^4 is a group $-OC(O)-$ or $-NHC(O)-$), can be prepared from a compound of formula III or IV:



(wherein X , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 are as defined hereinbefore and Y^7 is $-O-$ or $-NH-$), as appropriate, by standard acylation or coupling conditions including, for example, treatment of a compound of formula III or IV with a substituted carboxylic acid in the presence of a

coupling agent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and, optionally, a base such as an organic base for example triethylamine in a solvent such as an aprotic solvent for example dimethylformamide or in a chlorinated solvent for example trichloromethane or dichloromethane at a temperature in the range from 5 about -30°C to about 60°C, conveniently at or near ambient temperature.

(b) In another general example a compound of formula I, in which R⁵ or R⁶ is a group Y⁴R³⁵ (wherein R³⁵ is C₁₋₇alkoxy which may be substituted as defined hereinbefore and Y⁴ is a group -OC(O)- or -NHC(O)-), can be prepared from a compound of formula III and IV, as appropriate, by standard acylation reactions including, for example, treatment of a compound 10 of formula III or IV with a substituted alkylchloroformate in the presence of a base such as an organic base for example, triethylamine or *N*-methylmorpholine in a solvent such as an ether solvent for example tetrahydrofuran or in a chlorinated solvent for example dichloromethane at a temperature in the range from about -20°C to the reflux temperature of the solvent.

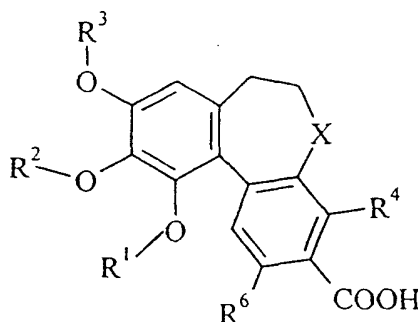
(c) In a further general example a compound of formula I, in which R⁵ or R⁶ is a group Y⁴R³⁵ 15 (wherein R³⁵ is aminoC₁₋₇alkylamino, C₁₋₇alkylaminoC₁₋₇alkylamino, di(C₁₋₇alkyl)aminoC₁₋₇alkylamino and may be substituted as defined hereinbefore, or is R⁵³ (wherein R⁵³ is as defined hereinbefore) and Y⁴ is a group -OC(O)- or -NHC(O)-), can be prepared from a compound of formula III or IV, as appropriate, by standard acylation reactions including, for example, treatment of a compound of formula III or IV with a substituted alkylisocyanate or a 20 carbamoyl chloride in the presence of a base such as an organic base for example triethylamine, pyridine or *N*-methylmorpholine in a solvent such as an ether solvent for example tetrahydrofuran or in a chlorinated solvent for example dichloromethane at a temperature in the range from about -20°C to the reflux temperature of the solvent.

(d) In a further example a compound of formula I, in which R⁵ or R⁶ is a group Y⁴R³⁵ 25 (wherein R³⁵ is a sugar moiety and Y⁴ is a group -O- or -NH-), can be prepared from a compound of formula III or IV, as appropriate, by standard glycosylation reactions including for example treatment of a compound of formula III or IV with a suitably protected 1-bromo sugar in a solvent such as a chlorinated solvent for example trichloromethane or an aromatic solvent for example toluene at a temperature in the range from about 0°C to the reflux 30 temperature of the solvent, followed by deprotection. Suitable protecting groups include acetyl groups for the sugar hydroxyl groups and esters for sugar carboxylic acids.

(e) In a further example a compound of formula I in which R^5 or R^6 is a group Y^4R^{35} (wherein R^{35} is sulphate and Y^4 is a group -O- or -NH-), can be prepared from a compound of formula III or IV, as appropriate, by standard sulphonylation reactions including for example treatment of a compound of formula III or IV with chlorosulphonic acid in the presence of a base such as dimethylaniline in a chlorinated solvent such as trichloromethane at a temperature in the range from about -20°C to about 60°C, or more preferably with chlorosulphonic acid in pyridine at a temperature in the range from about -20°C to about 60°C.

(f) In a further example a compound of formula I in which R^5 or R^6 is a group Y^4R^{35} (wherein R^{35} is C_{1-7} alkylphosphate and may be substituted as defined hereinbefore and Y^4 is a group -O- or -NH-), can be prepared from a compound of formula III or IV, as appropriate, by standard phosphorylation reactions including for example treatment of a compound of formula III or IV with phosphorus oxychloride in the presence of a base such as triethylamine in a chlorinated solvent such as trichloromethane at a temperature in the range from about -20°C to about 60°C, followed by treatment with an alcohol, or more preferably with alkyl dichlorophosphate in the presence of a base such as lithiumHMDS in THF at a temperature in the range from about -20°C to about 60°C, followed by treatment with water.

(g) Compounds of formula I in which R^5 is amino can be prepared from carboxylic acids of formula V:



(V)

(wherein X, R^1 , R^2 , R^3 , R^4 and R^6 are as defined hereinbefore) via Curtius rearrangement and hydrolysis (V. Fernholz Justus Liebigs Ann., 1950, 568, 63-72).

(h) Compounds of formula I may also be prepared from other compounds of formula I by chemical modification. Examples of such chemical modifications that may be applied are standard alkylation, arylation, heteroarylation, acylation, thioacylation, sulphonylation, sulphation, phosphorylation, aromatic halogenation and coupling reactions. These reactions

may be used to add new substituents or to modify existing substituents. Alternatively, existing substituents in compounds of formula I may be modified by, for example, oxidation, reduction, elimination, hydrolysis or other cleavage reaction to yield other compounds of formula I.

- 5 (i) A compound of formula I in which R⁵ or R⁶ is chloro may be prepared from a compound of formula III or IV by standard processes such as the Sandmeyer reaction.

Thus for example a compound of formula I containing an amino group may be acylated on the amino group by treatment with, for example, an acyl halide or anhydride in the presence of a base, for example a tertiary amine base such as triethylamine, in for
10 example, a solvent such as a hydrocarbon solvent e.g. dichloromethane at a temperature in the range for example -30°C to 120°C, conveniently at or near ambient temperature.

In another general example of an interconversion process an amino group in a compound of formula I may be sulphonylated by treatment with, for example, an alkyl or aryl sulphonyl chloride or an alkyl or aryl sulphonic anhydride in the presence of a base, for
15 example a tertiary amine base such as triethylamine, in for example a solvent such as a hydrocarbon solvent e.g. dichloromethane at a temperature in the range for example -30°C to 120°C, conveniently at or near ambient temperature.

In a further general example a compound of formula I containing a hydroxy group can be converted into the corresponding dihydrogenphosphate ester by treatment with for example
20 di-tert-butyl diisopropylphosphoramidite or di-tert-butyl diethylphosphoramidite in the presence of a suitable catalyst for example tetrazole in a solvent such as an ether solvent for example tetrahydrofuran at a temperature in the range -40°C to 40°C, conveniently at or near ambient temperature, followed by treatment with an oxidising agent for example 3-chloroperoxy benzoic acid at a temperature in the range -78°C to 40°C preferably -40°C to
25 10°C. The resulting intermediate phosphate triester is treated with an acid for example trifluoroacetic acid in a solvent such as a chlorinated solvent e.g. dichloromethane at a temperature in the range -30°C to 40°C conveniently at or near 0°C to give the compound of formula I containing a dihydrogenphosphate ester.

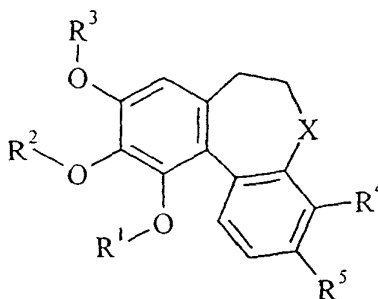
In a further general example a compound of formula I containing an amide can be
30 hydrolysed by treatment with for example an acid such as hydrochloric acid in a solvent such as an alcohol, for example methanol at an elevated temperature conveniently at the reflux temperature.

In another general example an O-alkyl group may be cleaved to the corresponding alcohol (OH) by reaction with boron tribromide in a solvent such as a chlorinated solvent e.g. dichloromethane at a low temperature e.g. around -78°C .

In a further general example compounds of formula I may be alkylated by reaction
 5 with a suitable alkylating agent such as an alkyl halide, an alkyl toluenesulphonate, an alkyl methanesulphonate or an alkyl triflate. The alkylation reaction can be carried out in the presence of a base for example an inorganic base such as a carbonate e.g. caesium or potassium carbonate, a hydride such as sodium hydride or an alkoxide such as potassium t-butoxide in a suitable solvent such as an aprotic solvent e.g. dimethylformamide or an ether
 10 solvent such as tetrahydrofuran at a temperature of around -10°C to 80°C .

Synthesis of Intermediates

(i) Compounds of formula III or IV, used as starting materials for the preparation of compounds of the invention are either known or can be prepared from known compounds by the application of standard procedures of organic synthesis known in the art. For example a
 15 compound of formula VI:



(VI)

20 (wherein X, R^1 , R^2 , R^3 , R^4 and R^5 are as defined hereinbefore), can be converted into a compound of formula IV where Y^7 is NH by the sequential application of standard nitration conditions followed by reduction of the incorporated nitro group under standard reduction conditions. Suitable nitration conditions include, for example, treatment with concentrated nitric acid in a solvent such as glacial acetic acid at a temperature from about -40°C to about
 25 40°C . Suitable reduction conditions include, for example, treatment with tin(II) chloride in a solvent such as hydrochloric acid, with or without an alcoholic cosolvent, at a temperature between ambient temperature and about 100°C .

(ii) Compounds of formulae III or IV can also be prepared from other compounds of formulae III or IV by chemical modification. For example a compound of formula IV in which Y⁷ is NH can be converted into the corresponding compound in which Y⁷ is O by treatment with sodium nitrite in sulphuric acid at around 0°C followed by heating to around 100°C.

- 5 Preparation of a compound of formula I as a single enantiomer or, where appropriate, diastereomer may be effected by synthesis from an enantiomerically pure starting material or intermediate or by resolution of the final product in a conventional manner.

Acid addition salts of the compounds of formula I are prepared in a conventional manner by treating a solution or suspension of the free base I with about one equivalent of a
10 pharmaceutically acceptable acid. Salts of compounds of formula I derived from inorganic or organic bases are prepared in a conventional manner by treating a solution or suspension of the free acid I with about one equivalent of a pharmaceutically acceptable organic or inorganic base. Alternatively both acid addition salts and salts derived from bases may be prepared by treatment of the parent compound with the appropriate ion-exchange resin in a standard
15 fashion. Conventional concentration and recrystallisation techniques are employed in isolating the salts.

(iii) Compounds of formula V may be prepared from the corresponding colchicine derivatives by treatment with sodium methoxide in methanol followed by ester hydrolysis with aqueous acid or aqueous base (V. Fernholz Justus Liebigs Ann., 1950, 568, 63-72). Compounds of
20 formula VI may be prepared by any of the methods described for compounds of formula I.

Many of the intermediates defined herein, for example, those of the formulae III, IV, V, and VI are novel and these are provided as a further feature of the invention. The preparation of these compounds is as described herein and/or is by methods well known to persons skilled in the art of organic chemistry.

- 25 Compounds according to the invention are able to destroy vasculature that has been newly formed such as tumour vasculature while leaving unaffected normal, mature vasculature. The identification of compounds which selectively, and preferably potently, damage newly-formed vasculature is desirable and is the subject of the present invention. The ability of the compounds to act in this way may be assessed, for example, using one or more
30 of the procedures set out below:

(a) Activity against tumour vasculature measured by radioactive tracer

This assay demonstrates the ability of compounds to damage selectively tumour vasculature.

Subcutaneous CaNT tumours were initiated by injecting 0.05ml of a crude tumour cell suspension, approximately 10^6 cells, under the skin overlying the rear dorsum of 12-16 week-old mice. The animals were selected for treatment after approximately 3-4 weeks, when their tumours reached a geometric mean diameter of 5.5-6.5 mm. Compounds were dissolved in sterile saline and injected intraperitoneally in a volume of 0.1 ml per 10g body weight. Tumour perfusion was measured 6 hours after intraperitoneal administration in tumour, kidney, liver, skin, muscle, gut and brain by the $^{86}\text{RbCl}$ extraction technique (Sapirstein, Amer. Jnl. Physiol., 1958, 193, 161-168). Tissue radioactivity measured 1 minute after an intravenous injection of $^{86}\text{RbCl}$ was used to calculate relative blood flow as a proportion of cardiac output (Hill and Denekamp, Brit. Jnl. Radiol., 1982, 55, 905-913). Five animals were used in control and treated groups. Results were expressed as a percentage of the blood flow in the corresponding tissues in vehicle treated animals.

15 (b) Activity against tumour vasculature measured by fluorescent dye

This assay demonstrates the ability of compounds to damage tumour vasculature.

Tumour functional vascular volume in CaNT tumour-bearing mice was measured using the fluorescent dye Hoechst 33342 according to the method of Smith et al (Brit. Jnl. Cancer 1988, 57, 247-253). Five animals were used in control and treated groups. The fluorescent dye was dissolved in saline at 6.25mg/ml and injected intravenously at 10mg/kg 24 hours after intraperitoneal drug treatment. One minute later, animals were killed and tumours excised and frozen; 10µm sections were cut at 3 different levels and observed under UV illumination using an Olympus microscope equipped with epifluorescence. Blood vessels were identified by their fluorescent outlines and vascular volume was quantified using a point scoring system based on that described by Chalkley, (Jnl. Natl. Cancer Inst., 1943, 4, 47-53). All estimates were based on counting a minimum of 100 fields from sections cut at the 3 different levels.

The ability of the compounds to bind to preparations of mammalian tubulin can be evaluated by a number of methods available in the literature, for example by following temperature initiated tubulin polymerisation by turbidity in the absence and presence of the compound (for example O.Boye *et al* Med. Chem. Res., 1991, 1, 142-150).

The activity of *N*-[3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide, (V. Fernholz Justus Liebigs Ann., 1950, 568, 63-72), against tumour vasculature was measured by the fluorescent dye method described above. This compound decreased perfused vascular volume by 88% relative to control when dosed at 50mg/kg intraperitoneally. The IC₅₀ of this compound in a tubulin polymerisation assay was 58 micromolar (O.Boye *et al* Med. Chem. Res., 1991, 1, 142-150).

The activity of compounds Examples 2 and 3 (described hereinafter) against tumour vasculature was measured by the fluorescent dye method described hereinbefore.

10 Compound of Example	% Decrease in vascular volume
2	95
3	45

15 (c) HUVEC detachment assay

This assay examined the effects of compounds on the adherence of HUVECs to tissue culture plasticware.

HUVECs were plated in 0.2% gelatin-coated 12 well tissue culture plates at a concentration of 3×10^4 cells per well in 1ml TCS medium. After 24 hours, when the cells were at ~30% confluency, the cells were dosed with compound for 40 minutes at 37°C, 5% CO₂. After this incubation the medium containing drug was pipetted off, and the cells were then gently washed in 2mls of HBSS (Hanks' Balanced Salt Solution purchased from Life Technologies Ltd, Paisley UK; Catalogue # 24020-083) to remove any detached cells. The washing solution was then removed, and the adherent cells remaining were trypsinised using 300µl of 1x Trypsin-EDTA solution (Life Technologies Ltd, Paisley, UK; Catalogue # 43500-019) at ambient temperature for 2 minutes. The trypsinised cells were then made up to 1ml with TCS Biologicals medium, then centrifuged at 2000rpm for 2 minutes. The cell pellet was then resuspended in a volume of 50µl of TCS Biologicals medium. Total cell counts were obtained by counting the cells on a haemocytometer. The amount of cell detachment was calculated by comparing the number of cells remaining attached following treatment with the number in undosed control wells.

(d) Hras5 necrosis model

NIH 3T3 fibroblasts transfected with Harvey ras, clone 5, (Hras5 cells) were kept in continual passage in Dulbecco's modified Eagles medium (DMEM) containing 10% foetal bovine serum (FBS) and 1% glutamine, at 37°C in a humidified incubator gassed with 7.5% carbon dioxide and 92.5% oxygen. Cells were implanted subcutaneously into the left flank of male nude mice (8-10 weeks of age) at an inoculum of 2×10^5 cells/mouse. Tumours were measured using calipers and randomised into groups of 2-4 mice between days 9-14 after implant. Mice were dosed with compounds, either intravenously or intraperitoneally, once on day of randomisation and culled 24 hours after dosing. Compounds were dissolved in 20% hydroxypropyl beta cyclodextrin in physiological saline at pH 7 and dosed in a volume of 0.1ml per 10g body weight. Tumours were excised, weighed and placed in buffered formalin. Area of necrosis in individual tumours was assessed from a haematoxylin/eosin stained-slide by a pathologist and scored from 0, meaning no significant change, to 10, meaning 91-100% necrosis.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula I as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for nasal administration or administration by inhalation, for example as a powder or solution, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream or for rectal administration for example as a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compositions of the present invention are advantageously presented in unit dosage form. The compound will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000mg per square metre body area of the animal, i.e. approximately 0.1-100mg/kg. A unit dose in the range, for example, 1-100mg/kg, preferably 1-50mg/kg is envisaged and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250mg of active ingredient.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50mg/kg is employed. However the daily dose will necessarily be
5 varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore for use
10 in a method of treatment of the human or animal body by therapy.

A further feature of the present invention is a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament, conveniently a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament for producing a vascular damaging effect in a warm-blooded animal such as a human being.

15 Thus according to a further aspect of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of a vascular damaging effect in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method for
20 producing a vascular damaging effect in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore.

The antiangiogenic treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances
25 and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the antiangiogenic treatment defined hereinbefore may
30 be: surgery, radiotherapy or chemotherapy. Such chemotherapy may include the following categories of therapeutic agent:

- (i) other antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function, angiostatin, endostatin, razoxin, thalidomide) and including vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (RTKIs) (for example those described in International Patent Applications Publication Nos. WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 the entire disclosure of which documents is incorporated herein by reference);
- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), antiprogestogens, antiandrogens
- 10 (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5 α -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for
- 15 example epidermal growth factor (EGF), platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);
- (iii) biological response modifiers (for example interferon);
- (iv) antibodies (for example edrecolomab); and
- 20 (v) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example
- 25 cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimetotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide,
- 30 amsacrine, topotecan, irinotecan).

As stated above the compounds defined in the present invention are of interest for their vascular damaging effects. Such compounds of the invention are expected to be useful

in the prophylaxis and treatment of a wide range of disease states where inappropriate angiogenesis occurs including cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin.

In addition to their use in therapeutic medicine, the compounds of formula I and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of in vitro and in vivo test systems for the evaluation of the effects of vascular damaging agents in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

It is to be understood that where the term "ether" is used anywhere in this specification it refers to diethyl ether.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum attainable;

(iv) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

Abbreviations

1,3-Dicyclohexylcarbodiimide	DCCI
4-Dimethylaminopyridine	DMAP
Tetrahydrofuran	THF
Diethyl azodicarboxylate	DEAD
5 <i>N,N</i> -Dimethylformamide	DMF
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride	EDCI
Dimethyl sulphoxide	DMSO
Trifluoroacetic acid	TFA
10 1,1,1,3,3,3-hexamethyldisilazane	HMDS

Example 1

N-[3-((*N*-benzyloxycarbonylalanyl)amino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-
dibenzo[*a,c*]cyclohepten-5-yl]acetamide

- 15 A solution of *N*-benzyloxycarbonyl-(*L*)-alanine (63mg, 0.28mmol) in dichloromethane (4ml) at -20°C was treated with *N*-[3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-
dibenzo[*a,c*]cyclohepten-5-yl]acetamide (100mg, 0.28mmol), (V. Fernholz Justus Liebigs
Ann., 1950, 568, 63-72), and 1,3-dicyclohexylcarbodiimide (134mg, 0.31mmol) and the
solution stirred for 16 hours at ambient temperature. Solvent was evaporated under reduced
20 pressure and the residue chromatographed on silica gel, eluting with ethyl acetate to give a
white solid which was triturated with diethyl ether. The title compound (85mg) was obtained
as a white solid.
m.p. 140-141°C
m/e 561

25

Example 2

N-[3-(alanylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-
yl]acetamide

- A solution of *N*-[3-((*N*-benzyloxycarbonylalanyl)amino)-9,10,11-trimethoxy-6,7-
30 dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (70mg, 0.125mmol), (prepared as
described in Example 1), in ethanol (2ml) was hydrogenated at atmospheric pressure over 5%
palladium on carbon (10mg) for 2 hours. Ethanol (3ml) was added and the solution was

filtered through diatomaceous earth and the filtrate concentrated under reduced pressure.

Trituration with ethyl acetate/diethyl ether gave the title compound (35mg) as a white solid.

m.p. 170-173°C

m/e 427

5

Example 3

N-[3-(4-(1-piperidinyl)piperidinylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5yl]acetamide

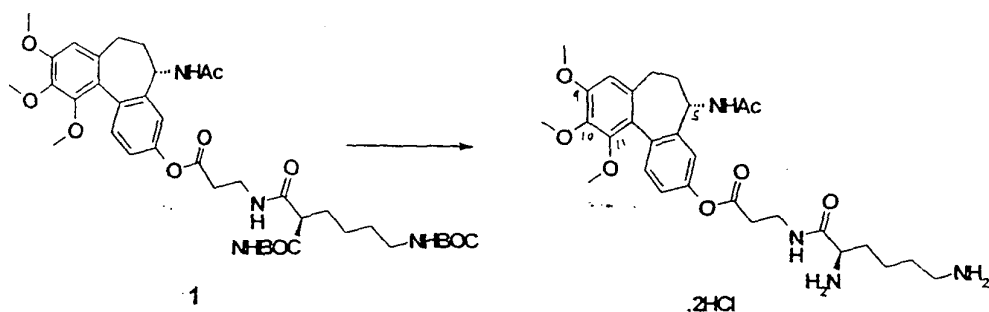
A solution of *N*-acetyl-colchicol (300mg, 0.84mmol), (J. Cech F. Santacy Collect.

10 Czech Comm 1949, 4, 532-539), in pyridine (5ml) was treated with 4-piperidinopiperidine carbamoyl chloride (346mg, 1.5mmol), (K.H.Henegar et al. J.Org. Chem., 1997, 62, 6588-6597) and the solution heated at reflux for 1 hour. The cooled mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified on silica gel eluting with methanol to give the title compound (180mg) as a white solid.

15 m.p. 168-175°C

m/e 551

Example 4



20

A solution of (5*S*)-5-(acetlamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-[(2*R*)-2,6-di(*tert*butoxycarbonylamino)hexanoyl]amino}propanoate (1) (0.123 g ; 0.162 mmol) in dichloromethane (10 ml) was treated with a 4.8M solution of hydrogen chloride in ether (170
25 μ l ; 0.81 mmol). The mixture was stirred at ambient temperature for 1 hour and the resulting precipitate was filtered, washed with ether and dried to give (5*S*)-5-(acetlamino)-9,10,11-

trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-{{(2*R*)-2,6-diaminohexanoyl]amino}propanoate as a white solid.

Yield : 84%

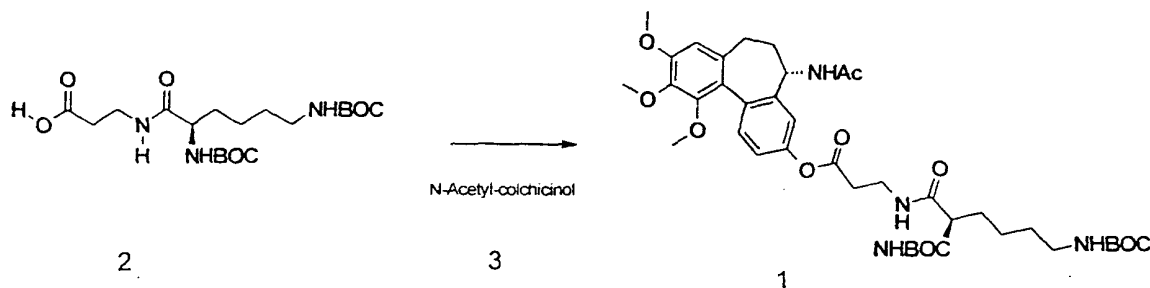
¹H NMR spectrum (DMSO-d₆) : 1.39 (m, 2H) ; 1.58 (m, 2H) ; 1.74 (m, 2H) ; 1.89 (s, 3H) ;

5 1.89 (m, 1H) ; 2.02 (m, 1H) ; 2.15 (m, 1H) ; 2.5 (m, 1H, signal obscured partially by DMSO peak) ; 2.74 (m, 2H) ; 2.84 (t, 2H) ; 3.52 (m, 5H) ; 3.78 (s, 3H) ; 3.78 (m, 1H) ; 3.84 (s, 3H) ; 4.55 (m, 1H) ; 6.80 (s, 1H) ; 7.1-7.15 (m, 2H) ; 7.35 (dd, 1H) ; 8.01 (br s, 2H) ; 8.32 (m, 2H) ; 8.53 (d, 1H) ; 8.96 (t, 1H).

MS-ESI : 557 [MH]⁺

10	Elemental analysis :	Found	C 53.8	H 6.8	N 8.7
	C ₂₉ H ₄₀ N ₄ O ₇ ; 0.8 H ₂ O, 2 HCl	Requires	C 53.9	H 7.2	N 8.1%

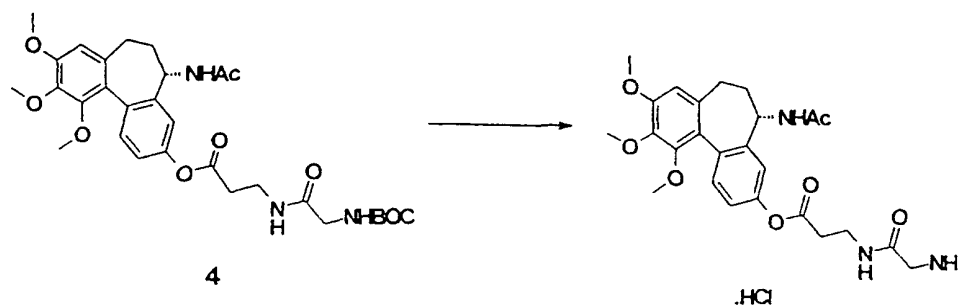
The starting material was prepared as follows:



A mixture of 3-{{(2*R*)-2,6-di(*tert*butoxycarbonylamino)hexanoyl]amino}propanoic acid (2) (0.178 g ; 0.5 mmol), DCCl (0.124 g ; 0.6 mmol), DMAP (0.013 g ; 0.1mmol) and *N*-acetyl-colchicinol (0.25 g ; 1.2 mmol) in dichloromethane was stirred under argon atmosphere
20 at ambient temperature for 5 hours. After filtration of the insoluble material the residue was purified by flash chromatography eluting with dichloromethane/ethanol (95/5) to give (1).

Yield : 32%

¹H NMR spectrum (DMSO-d₆) : 1.15-1.6 (m, 6H) ; 1.36 (s, 18H) ; 1.87 (s, 3H) ; 1.87 (m, 1H) ; 2.05 (m, 1H) ; 2.15 (m, 1H) ; 2.50 (m, 1H, signal obscured partially by DMSO peak) ; 2.75 (t, 2H) ; 2.86 (m, 2H) ; 3.85 (m, 2H) ; 3.51 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 3.85 (m, 1H) ;
25 4.55 (m, 1H) ; 3.7-3.8 (m, 2H) ; 6.8 (s, 1H) ; 7.08 (s, 1H) ; 7.1 (m, 1H) ; 7.32 (dd, 1H) ; 8.01 (t, 1H) ; 8.35 (d, 1H).

Example 5

5

A solution of (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-[(2-*tert*butoxycarbonylaminoacetyl)amino]propanoate (4) (0.36 g ; 0.61 mmol) in dichloromethane (5 ml) was treated with a 4.8M solution of hydrogen chloride in ether (1 ml). The mixture was stirred at ambient temperature for 1 hour. After

10 dilution with ether, the resulting precipitate was filtered, washed with ether and dried to give (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-[(2-aminoacetyl)amino]propanoate.

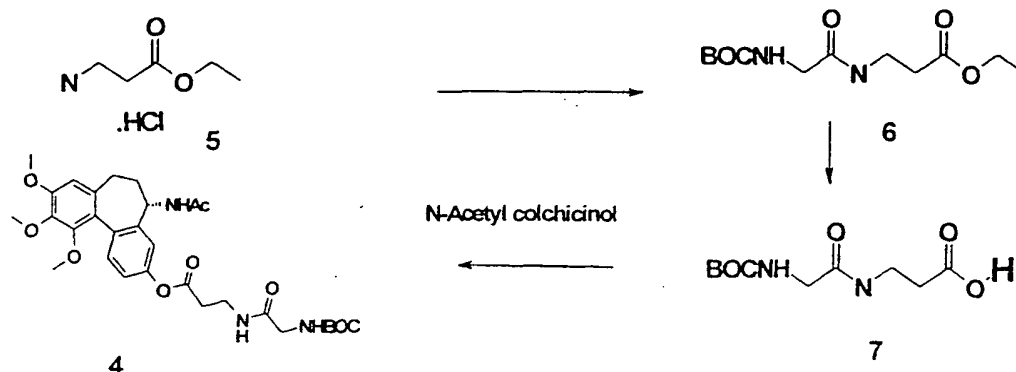
Yield : 98%

¹H NMR spectrum (DMSO-*d*₆) : 1.90 (m, 1H) ; 1.90 (s, 3H) ; 2.05 (m, 1H) ; 2.3 (m, 1H) ; 2.9 (m, 1H, signal obscured partially by DMSO peak) ; 2.84 (t, 2H) ; 3.52 (s, 3H) ; 3.52 (m, 2H) ; 3.6 (m, 2H, signal obscured partially by H₂O peak) ; 3.8 (s, 3H) ; 3.86 (s, 3H) ; 4.55 (m, 1H) ; 6.82 (s, 1H) ; 7.13 (m, 2H) ; 7.37 (dd, 1H) ; 8.1 (br s, 2H) ; 8.46 (d, 1H) ; 8.67 (t, 1H).

MS-ESI : 486 [MH]⁺

Elemental analysis :	Found	C 54.8	H 6.2	N 7.7
20 C ₂₅ H ₃₁ N ₃ O ₇ ; 0.8 H ₂ O, 1.3 HCl	Requires	C 54.8	H 6.3	N 7.6%

The starting material was prepared as follows:



A solution of β -alanine ethyl ester hydrochloride salt (5) (3.07 g ; 0.02 mmol), *N*-(*tert*butoxycarbonyl)glycine (3.5 g ; 0.02 mmol), DCCl (4.12 g ; 0.02mmol) and 4-methylmorpholine (2.2 ml) in dichloromethane (60 ml) was stirred overnight under argon atmosphere at ambient temperature. After filtration the residue was purified by flash chromatography eluting with dichloromethane/ethanol (96/4) to give ethyl 3-[(2-*tert*butoxycarbonylaminoacetyl)amino]propanoate (6).

Yield : 62%

¹H NMR spectrum (CDCl₃) : 1.27 (t, 3H) ; 1.45 (s, 9H) ; 3.55 (m, 2H) ; 3.77 (d, 2H) ; 4.15 (q, 2H) ; 5.3 (br s, 2H) ; 6.56 (br s, 2H).

A solution of (6) at 0°C (3.43 g ; 0.012 mmol) in methanol (40 ml) was treated with 2N sodium hydroxide (6.9 ml ; 0.013 mmol). The mixture was stirred at ambient temperature for 90 minutes. After evaporation of the methanol and removal of the insoluble material by filtration, the solution was adjusted to pH5 with 6N hydrochloric acid. The mixture was extracted with dichloromethane and the organic layer evaporated to dryness to give 3-[(2-*tert*butoxycarbonylaminoacetyl)amino]propanoic acid (7).

Yield : 16%

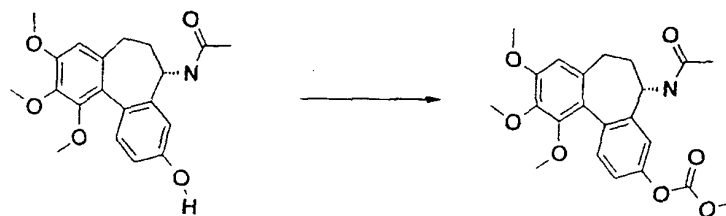
¹H NMR spectrum (CDCl₃ + CD₃CO₂D) : 1.44 (s, 9H) ; 2.61 (t, 2H) ; 3.5 (m, 2H) ; 3.80 (m, 2H).

A mixture of *N*-acetyl-colchicinol (0.357 g ; 1 mmol), DCCl (0.248 g ; 1.2 mmol), DMAP (0.025 g ; 0.2 mmol) and (7) (0.246 g ; 1 mmol) in dichloromethane (7 ml) was stirred under argon atmosphere for 5 hours. After removal of the insoluble material by filtration the residue was purified by flash chromatography eluting with dichloromethane/ethanol (92/8) to give (4) as a foam.

Yield : 61%

¹H NMR spectrum (DMSO-d₆) : 1.4 (s, 9H) ; 1.89 (s, 3H) ; 1.89 (m, 1H) ; 2.07 (m, 1H) ; 2.18 (m, 1H) ; 2.5 (m, 1H, signal obscured partially by DMSO peak) ; 2.77 (t, 2H) ; 3.45 (m, 2H) ; 3.52 (s, 3H) ; 3.5 (m, 2H) ; 3.8 (s, 3H) ; 3.85 (s, 3H) ; 4.55 (m, 1H) ; 6.81 (s, 1H) ; 6.97 (t, 1H) ; 7.11 (m, 2H) ; 7.35 (dd, 1H) ; 8.01 (t, 1H) ; 8.38 (d, 1H).

Example 6



10

Triethylamine (70 µl ; 0.5 mmol) and methyl chloroformate (39 µl ; 0.5 mmol) were added to a solution of *N*-acetyl-colchicine (0.178 g ; 0.5 mmol) in THF (3 ml). The mixture was stirred at ambient temperature for 90 minutes. After removal of the insoluble material by filtration the residue was purified by flash chromatography eluting with dichloromethane/ethanol (98/2) to give **(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl methyl carbonate**.

Yield : 75%

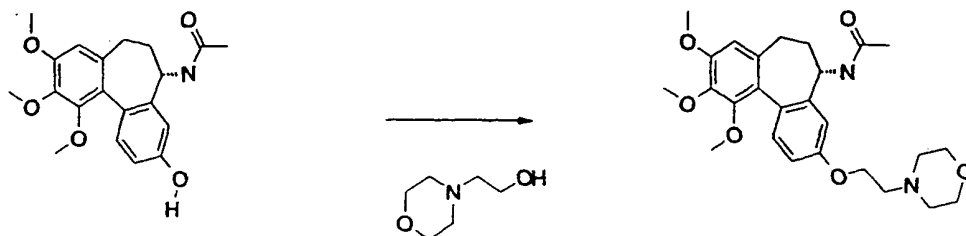
¹H NMR spectrum (DMSO-d₆) : 1.87 (s, 3H) ; 1.87 (m, 1H) ; 2.05 (m, 1H) ; 2.17 (m, 1H) ; 2.5 (m, 1H, signal obscured partially by DMSO peak) ; 3.52 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 3.85 (s, 3H) ; 4.52 (m, 1H) ; 6.8 (s, 1H) ; 7.16-7.18 (m, 2H) ; 7.36 (dd, 1H) ; 8.38 (d, 1H).

MS-ESI : 438 [MH]⁺

Elemental analysis :	Found	C 61.7	H 6.2	N 3.3
C ₂₂ H ₂₅ NO ₇ ; 0.7 H ₂ O	Requires	C 61.6	H 6.2	N 3.4%

25

Example 7



DEAD (0.118 g ; 0.75 mmol), triphenylphosphine (0.196 g ; 0.75 mmol) and 4-(2-hydroxyethyl)morpholine (61 μ l ; 0.5 mmol) were added to a solution of *N*-acetyl-colchicinol (0.178 g ; 0.5 mmol) in dichloromethane (5 ml) under argon atmosphere. The mixture was stirred at ambient temperature for 6 hours. After evaporation the residue was purified by flash chromatography eluting with a gradient of 2-10% ethanol/dichloromethane to give *N*-[(5*S*)-3-(2-morpholinoethoxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide.

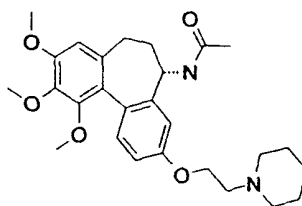
Yield : 37%

¹H NMR spectrum (DMSO-*d*₆) : 1.85 (m, 1H) ; 1.87 (s, 3H) ; 2.05 (m, 1H) ; 2.15 (m, 1H) ; 2.39 (m, 2H) ; 2.5 (m, 3H, signal obscured partially by DMSO peak) ; 2.72 (t, 2H) ; 3.46 (s, 3H) ; 3.54-3.6 (s, 4H) ; 3.77 (s, 3H) ; 3.82 (s, 3H) ; 4.09-4.12 (m, 2H) ; 4.55 (m, 1H) ; 6.76 (s, 1H) ; 6.86-6.90 (m, 2H) ; 7.23 (dd, 2H) ; 8.35 (d, 1H).

MS-ESI : 471 [MH]⁺

Elemental analysis :	Found	C 66.4	H 7.3	N 6.0
C ₂₆ H ₃₄ N ₂ O ₆	Requires	C 66.6	H 7.3	N 6.3%

20 Example 8



Using an analogous procedure to that described for Example 7, *N*-acetyl-colchicinol was reacted with 4-(2-hydroxyethyl)piperidine to give *N*-[(5*S*)-3-(2-piperidinoethoxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide.

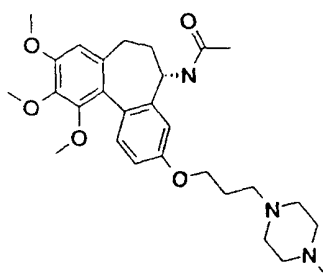
Yield : 20%

¹H NMR spectrum (DMSO-d₆) : 1.39 (m, 2H) ; 1.49 (m, 4H) ; 1.80 (m, 1H) ; 1.88 (s, 3H) ; 2.05 (m, 1H) ; 2.15 (m, 1H) ; 2.45 (m, 4H) ; 2.5 (m, 1H, signal obscured partially by DMSO peak) ; 2.67 (m, 2H) ; 3.46 (s, 3H) ; 3.77 (s, 3H) ; 3.82 (s, 3H) ; 4.08 (t, 2H) ; 4.55 (m, 1H) ; 5 6.76 (s, 1H) ; 6.86-6.9 (m, 2H) ; 7.22 (dd, 1H) ; 8.35 (d, 1H).

MS-ESI : 469 [MH]⁺

Elemental analysis :	Found	C 68.7	H 7.8	N 5.9
C ₂₇ H ₃₆ N ₂ O ₅ ; 0.2 H ₂ O	Requires	C 68.5	H 8.0	N 6.1%

10 Example 9



Using an analogous procedure to that described for Example 7, *N*-acetyl-colchicinol was reacted with 4-(3-hydroxypropyl)-1-methylpiperazine to give *N*-[(5*S*)-3-(3-(4-methylpiperazin-1-yl)propoxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-**15** dibenzo[*a,c*]cyclohepten-5-yl]acetamide.

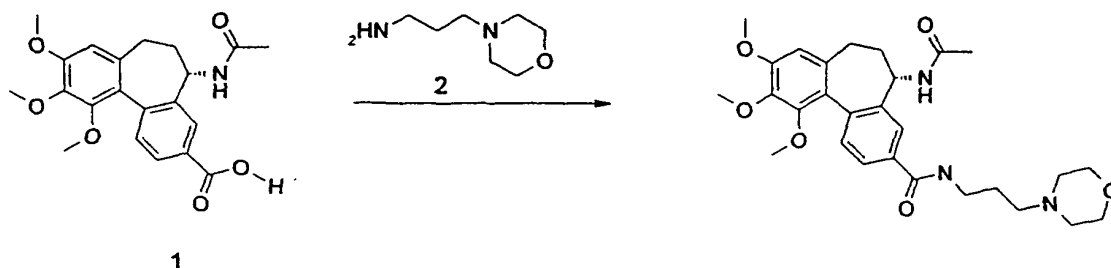
Yield : 22%

¹H NMR spectrum (DMSO d₆) : 1.88 (s, 3H) ; 1.85-1.9 (m, 3H) ; 2.04-2.16 (m, 5H) ; 2.32-2.53 (m, 11H, signals obscured partially by DMSO peak) ; 3.47 (s, 3H) ; 3.78 (s, 3H) ; 3.83 (s, **20** 3H) ; 4.03 (t, 2H) ; 4.55 (m, 1H) ; 6.72 (s, 1H) ; 6.85 (dd, 1H) ; 6.9 (m, 1H) ; 7.23 (d, 1H) ; 8.23 (d, 1H).

MS-ESI : 498 [MH]⁺

Elemental analysis :	Found	C 64.8	H 8.0	N 8.1
C ₂₈ H ₃₉ N ₃ O ₅ ; 0.8 H ₂ O,	Requires	C 64.7	H 7.7	N 8.2%

25 0.1 dichloromethane

Example 10

- 5 A solution of *N*-[(5*S*)-3-carboxy-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (0.3 g ; 0.779 mmol), (Med. Chem. Res. 1991, 142), DCCI (0.322 g ; 1.55 mmol), DMAP (0.069 g ; 0.389mmol) and 4-(3-aminopropyl)morpholine (170 μ l ; 1.17 mmol) in dichloromethane (6 ml) was stirred under argon atmosphere overnight. After removal of the insoluble material by filtration, the residue
- 10 was purified on reverse phase silica eluting with a gradient of 40-50% methanol/ammonium carbonate buffer (2 g/l, pH7). The appropriate fractions were evaporated to dryness and triturated in ether to give (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-*N*-(3-morpholinopropyl)-6,7-dihydro-5*H*-dibenzo[*a,c*]cycloheptene-3-carboxamide as a white solid.

15 Yield : 30%

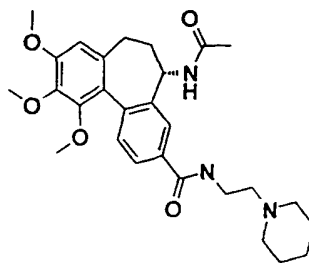
¹H NMR spectrum (DMSO-d₆) : 1.7 (m, 2H) ; 1.91 (s, 3H) ; 1.91 (m, 1H) ; 2.05 (m, 1H) ; 2.2 (m, 1H) ; 2.37 (m, 6H) ; 2.5 (m, 3H, signal obscured partially by DMSO peak) ; 3.51 (s, 3H) ; 3.58 (m, 4H) ; 3.8 (s, 3H) ; 3.86 (s, 3H) ; 4.58 (m, 1H) ; 6.83 (s, 1H) ; 7.39 (dd, 1H) ; 7.74 (m, 1H) ; 7.84 (s, 1H) ; 8.51 (m, 2H).

20 MS-ESI : 512 [MH]⁺

Elemental analysis :	Found	C 64.8	H 7.3	N 8.1
C ₂₈ H ₃₇ N ₃ O ₆ ; 0.4 H ₂ O	Requires	C 64.5	H 7.3	N 8.0%

Example 11

- 66 -



Using an analogous procedure to that described for Example 10, *N*-[(5*S*)-3-carboxy-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide was reacted with 1-(2-aminoethyl)piperidine to give (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-*N*-(2-piperidinoethyl)-6,7-dihydro-5*H*-dibenzo[*a,c*]cycloheptene-3-carboxamide.

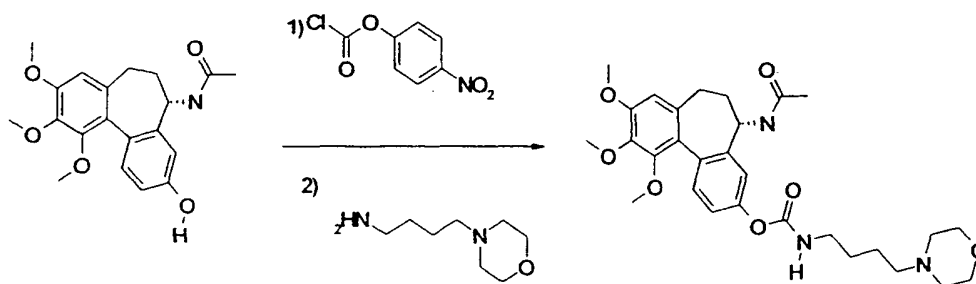
Yield : 43%

¹H NMR spectrum (DMSO-d₆) : 1.38 (m, 2H) ; 1.49 (m, 4H) ; 1.89 (s, 3H) ; 1.89 (m, 1H) ; 2.05 (m, 1H) ; 2.18 (m, 1H) ; 2.4-2.5 (m, 4H) ; 2.5 (m, 1H, signal obscured partially by DMSO peak) ; 3.38 (m, 4H) ; 3.49 (s, 3H) ; 3.79 (s, 3H) ; 3.84 (s, 3H) ; 4.58 (m, 1H) ; 6.81 (s, 1H) ; 7.37 (d, 1H) ; 7.71 (m, 1H) ; 7.81 (s, 1H) ; 8.35 (t, 1H) ; 8.49 (d, 1H).

MS-ESI : 496 [MH]⁺

Elemental analysis :	Found	C 66.4	H 7.6	N 8.3
C ₂₈ H ₃₇ N ₃ O ₅ ; 0.6 H ₂ O	Requires	C 66.1	H 7.7	N 8.3%

Example 12



A solution of *N*-acetyl-colchicine (0.357 g ; 1 mmol), 4-nitrophenyl chloroformate (0.262g; 1.3 mmol) and triethylamine (182 μl ; 1.3 mmol) in dichloromethane (10 ml) was stirred, under argon atmosphere, at ambient temperature for 90 minutes. 4-(4-Aminobutyl)morpholine (0.237g ; 1.5 mmol) was then added and the mixture was further

stirred for 4 hours. After evaporation to dryness the residue was purified by flash chromatography eluting with a gradient of 0-12% ethanol/dichloromethane to give (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl *N*-(4-morpholinobutyl)carbamate as a white foam.

5 Yield : 24%

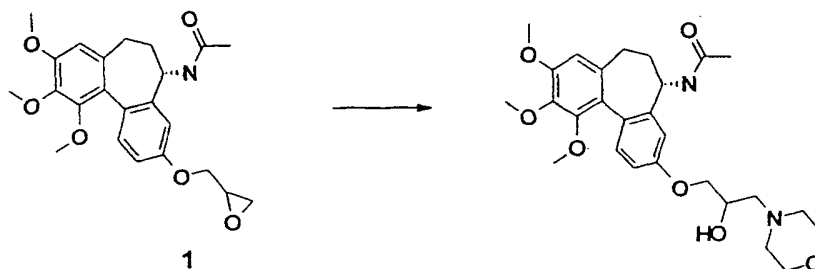
¹H NMR spectrum (DMSO-d₆) : 1.49 (m, 4H) ; 1.86 (s, 3H) ; 1.86 (m, 1H) ; 2.05 (m, 1H) ; 2.18 (m, 1H) ; 2.26-2.34 (m, 6H) ; 2.5 (m, 1H, signal obscured partially by DMSO peak) ; 3.08 (m, 2H) ; 3.51 (s, 3H) ; 3.57 (m, 4H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 4.55 (m, 1H) ; 6.79 (s, 1H) ; 7.02 (m, 2H) ; 7.29 (d, 1H) ; 7.78 (t, 1H) ; 8.39 (d, 1H).

10 MS-ESI : 542 [MH]⁺

Elemental analysis :	Found	C 63.5	H 7.3	N 7.7
C ₂₉ H ₃₉ N ₃ O ₇ ; 0.4 H ₂ O	Requires	C 63.4	H 7.3	N 7.7%

Example 13

15



A solution of *N*-[(5*S*)-3-(2,3-epoxypropoxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (1) (0.092 g ; 0.22 mmol) and morpholine (40 μl ; 0.44 mmol) in methanol was heated at reflux for 4 hours. After evaporation to dryness the residue was purified by flash chromatography eluting with dichloromethane/ethanol (90/10) to give *N*-[(5*S*)-3-(2-hydroxy-3-morpholinopropoxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide as a yellow foam.

Yield : 55%

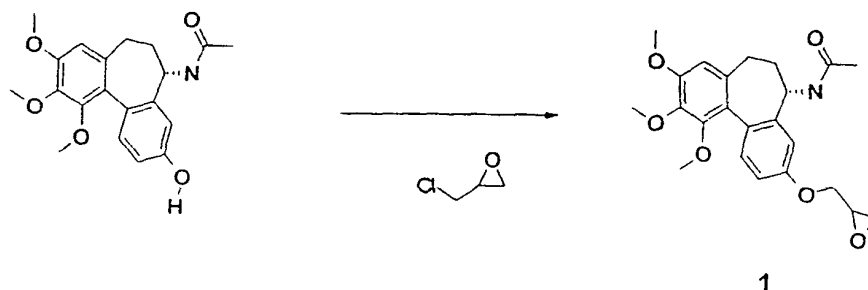
25 ¹H NMR spectrum (DMSO-d₆) : 1.88 (s, 3H) ; 1.88 (m, 1H) ; 2.05 (m, 1H) ; 2.15 (m, 1H) ; 2.42-2.5 (m, 4H) ; 2.5 (m, 1H, signal obscured partially by DMSO peak) ; 3.33-3.4 (m, 4H) ;

3.46 (s, 3H) ; 3.57 (m, 2H) ; 3.77 (s, 3H) ; 3.82 (s, 3H) ; 3.90 (m, 1H) ; 3.99 (m, 2H) ; 4.52 (m, 1H) ; 4.9 (t, 1H) ; 6.76 (s, 1H) ; 6.86-6.9 (m, 2H) ; 7.23 (d, 1H) ; 8.37 (d, 1H).

MS-ESI : 501 [MH]⁺

Elemental analysis :	Found	C 64.8	H 7.3	N 5.6
5 C ₂₇ H ₃₆ N ₂ O ₇	Requires	C 64.5	H 7.5	N 5.5%

The starting material was prepared as follows:



10

A solution of *N*-acetyl-colchicinol (0.179 g ; 0.5 mmol), potassium carbonate (0.083g; 0.6 mmol) and epichlorohydrin (0.059 g ; 0.75 mmol) in DMF (2 ml) was heated at 80°C for 5 hours. The mixture was poured into saturated sodium hydrogen carbonate and extracted with ethyl acetate. The organic phase was washed with brine, dried (MgSO₄) and evaporated to give an oil which was purified by flash chromatography eluting with a 2-4% gradient of ethanol/dichloromethane to give (1).

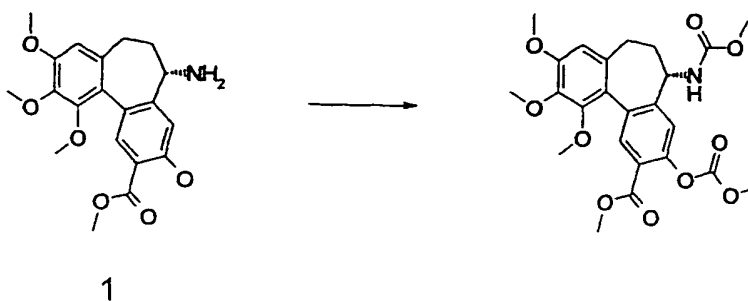
15

Yield : 46%

¹H NMR spectrum (DMSO-d₆) : 1.88 (s, 3H) ; 1.84 (m, 1H) ; 2.05 (m, 1H) ; 2.15 (m, 1H) ; 2.5 (m, 1H partially obscured by DMSO peak) ; 2.75 (m, 1H) ; 2.88 (m, 1H) ; 3.42 (m, 1H) ; 3.46 (s, 3H) ; 3.77 (s, 3H) ; 3.82 (s, 3H) ; 3.87 (m, 1H) ; 4.35 (m, 1H) ; 4.52 (m, 1H) ; 6.76 (s, 1H) ; 6.88-6.94 (m, 2H) ; 7.24 (d, 1H) ; 8.35 (d, 1H).

20

Example 14



A solution of methyl (5*S*)-9,10,11-trimethoxy-5-amino-3-hydroxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cycloheptene-2-carboxylate (1) (0.373 g; 1 mmol) methyl chloroformate (0.17 ml ; 2.2 mmol) and triethylamine was stirred at ambient temperature overnight. After

5 evaporation to dryness, the residue was purified by flash chromatography, eluting with ethanol/dichloromethane (2/98) and further purified by preparative HPLC on reverse phase silica eluting with methanol/ammonium carbonate buffer (2 g/l pH7) (50/50) to give **methyl (5*S*)-9,10,11-trimethoxy-5-[(methoxycarbonyl)amino]-3-[(methoxycarbonyl)oxy]-6,7-dihydro-5*H*-dibenzo[*a,c*]cycloheptene-2-carboxylate**.

10 Yield : 48 %

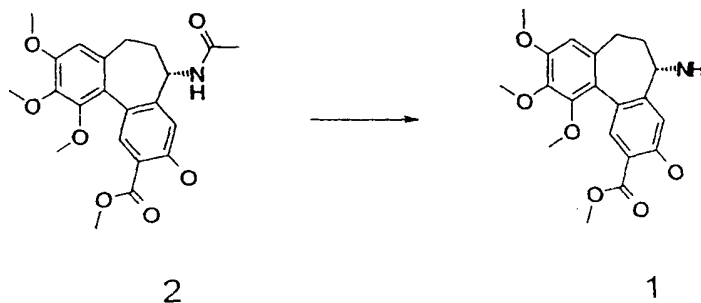
¹H NMR spectrum (DMSO-*d*₆) : 1.84-2.09 (m, 2H) ; 2.19-2.31 (m, 1H) ; 2.57 (m, 1H, partially obscured by DMSO peak) ; 3.50 (s, 3H) ; 3.55 (s, 3H) ; 3.81 (s, 3H) ; 3.82 (s, 3H) ; 3.86 (s, 3H) ; 3.87 (s, 3H) ; 4.28-4.389 (m, 1H) ; 6.85 (s, 1H) ; 7.24 (s, 1H) ; 7.88-7.97 (m, 1H) ; 7.91 (s, 1H).

15 MS-ESI : 512 [MNa]⁺

Elemental analysis	Found	C 58.7	H 5.7	N 3.0
C ₂₄ H ₂₇ NO ₁₀	Requires	C 58.9	H 5.6	N 2.9%

The starting material was prepared as follows:

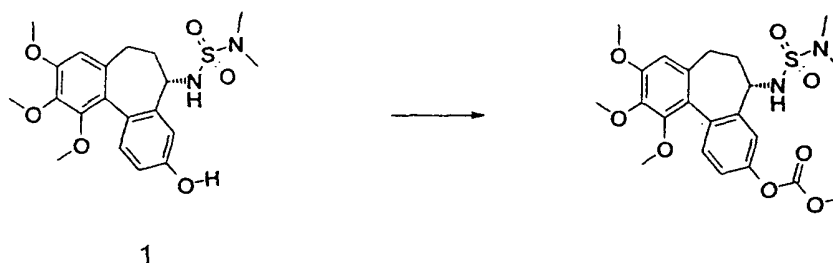
20



A solution of methyl (5*S*)-9,10,11-trimethoxy-5-acetylamino-3-hydroxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cycloheptene-2-carboxylate (2) (Collect. Czech. Chem. Communi. 64, 217 (1999)) in a mixture of 6*N* hydrochloric acid and methanol (30/70) was heated at reflux for 8 hours. The mixture was adjusted to pH8 by addition of sodium carbonate. Extraction with dichloromethane and purification by flash chromatography (elution with dichloromethane /methanol (94/6)) gave (1) as a foam.

¹H NMR spectrum (DMSO-d₆) : 1.61 (m, 1H) ; 2.04 (m, 1H) ; 2.28 (m, 1H) ; 2.45 (m, 1H) ; 3.50 (s, 3H) ; 3.54 (m, 1H) ; 3.77 (s, 3H) ; 3.83 (s, 3H) ; 3.90 (s, 3H) ; 6.77 (s, 1H) ; 7.30 (s, 1H) ; 7.73 (s, 1H) ; 1.57 (br s, 1H).

Example 15



15

A solution of (5*S*)-5-[[[(dimethylamino)sulphonyl]amino]-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-ol (1) (0.9 ; 0.71 mmol), methyl chloroformate (0.061 ml ; 0.782 mmol) and triethylamine (0.109 ml ; 0.782 mmol) in acetonitrile (8 ml) was stirred under argon atmosphere at 40°C for 4 hours. After evaporation to dryness, the residue was purified by flash chromatography eluting with ethanol/dichloromethane (2/98) to give (5*S*)-5-[[[(dimethylamino)sulphonyl]amino]-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl methyl carbonate.

Yield : 32 %

¹H NMR spectrum (DMSO-d₆) : 1.93-2.03 (m, 2H) ; 2.12-2.17 (m, 1H) ; 2.46 (s, 6H) ; 2.45-2.55 (m, 1H) ; 3.46 (s, 3H) ; 3.79 (s, 3H) ; 3.85 (s, 3H) ; 3.87 (s, 3H) ; 3.94-4.10 (m, 1H) ; 6.82 (s, 1H) ; 7.21 (d, 1H) ; 7.37 (d, 1H) ; 7.43 (s, 1H) ; 7.93 (br s, 1H).

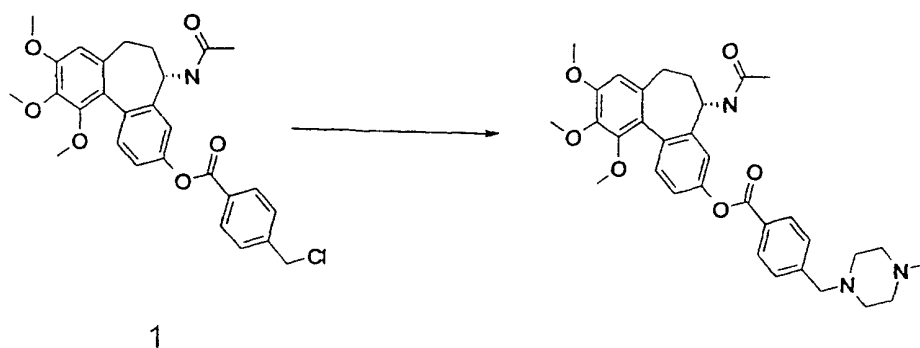
MS-ESI : 503 [MNa]⁺

- 71 -

Elemental analysis	Found	C 55.2	H 6.1	N 5.8	S 6.3
$C_{22}H_{28}N_2O_8S$	Requires	C 55.0	H 5.9	N 5.8	S 6.7%

Example 16

5



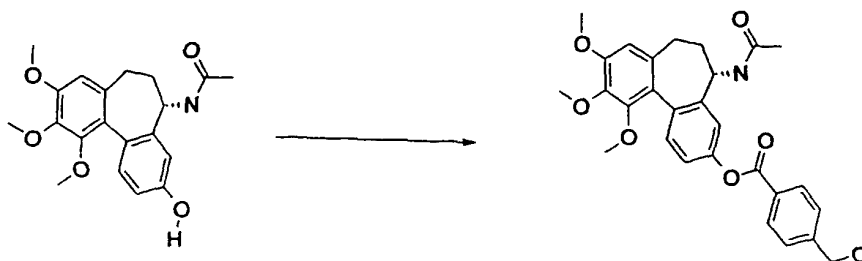
A solution of *N*-[(5*S*)-3-(4-chloromethylphenylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (1) (0.308 g ; 0.604 mmol), 1-methylpiperazine (0.088 ml ; 0.785 mmol) and sodium iodide (0.02 g ; 0.121 mmol) in acetonitrile (10 ml) was stirred under argon atmosphere overnight. After evaporation to dryness, the residue was purified by flash chromatography eluting with a 5-12 % gradient of methanol/dichloromethane. After evaporation of the appropriate fractions, the solid was triturated in ether/pentane to give *N*-[(5*S*)-3-(4-{4-methylpiperazin-1-ylmethyl}phenylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide as a solid.

Yield : 75 %

^1H NMR spectrum (DMSO-d_6) : 1.86 (s, 3H) ; 1.83-1.98 (m, 1H) ; 2.00-2.26 (m, 2H) ; 2.31 (br s, 3H) ; 2.4-2.6 (m, 8H) ; 2.53-2.59 (m, 1H) ; 3.54 (s, 3H) ; 3.62 (s, 2H) ; 3.80 (s, 3H) ; 3.85 (s, 3H) ; 4.53-4.64 (m, 1H) ; 6.82 (s, 1H) ; 7.20-7.25 (m, 2H) ; 7.41 (d, 1H) ; 7.56 (d, 2H) ; 8.13 (d, 2H) ; 8.39 (d, 1H).

MS-ESI : 574 [MH] $^+$

The starting material was prepared as follows



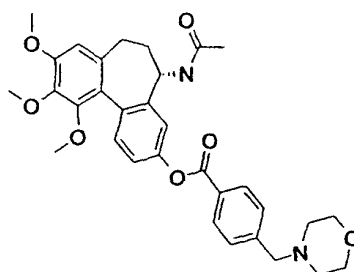
A solution of *N*-acetyl-colchicinol (0.357 g ; 1 mmol), EDCI (0.23 g ; 1.2 mmol), DMAP (0.025 g ; 0.2 mmol) and 4-chloromethylbenzoic acid (0.205 g ; 1.2 mmol) in
 5 dichloromethane (8 ml) was stirred under argon atmosphere overnight. After evaporation to dryness, the residue was purified by flash chromatography eluting with dichloromethane/ethanol (98/2) to give (1).

Yield : 72 %

¹H NMR spectrum (DMSO-d₆) : 1.86 (s, 3H) ; 1.91 (m, 1H) ; 1.04-2.14 (m, 1H) ; 2.14-2.67 (m,
 10 1H) ; 2.57 (m, 1H, partially obscured by DMSO peak) ; 3.54 (s, 3H) ; 3.80 (s, 3H) ; 3.86 (s, 3H) ; 4.54-4.64 (m, 1H) ; 4.91 (s, 2H) ; 6.83 (s, 1H) ; 7.21-7.28 (m, 2H) ; 7.42 (d, 1H) ; 7.70 (d, 2H) ; 8.14 (d, 2H) ; 8.40 (d, 1H).

Example 17

15



Using an analogous procedure to that described for Example 16, *N*-[(5*S*)-3-(4-chloromethylphenylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-
 20 dibenzo[*a,c*]cyclohepten-5-yl]acetamide was reacted with morpholine to give *N*-[(5*S*)-3-(4-{morpholinomethyl}phenylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide.

Yield : 86 %

¹H NMR spectrum (DMSO-d₆) : 1.90 (s, 3H) ; 1.88-2.01 (m, 1H) ; 2.06-2.30 (m, 2H) ; 2.43 (br s, 4H) ; 2.54-2.63 (m, 1H) ; 3.30 (m, 2H) ; 3.58 (s, 3H) ; 3.62-3.67 (m, 6H) ; 3.84 (s, 3H) ; 3.89 (s, 3H) ; 4.57-4.67 (m, 1H) ; 3.86 (s, 1H) ; 7.23-7.30 (m, 2H) ; 7.45 (d, 1H) ; 7.61 (d, 1H) ;

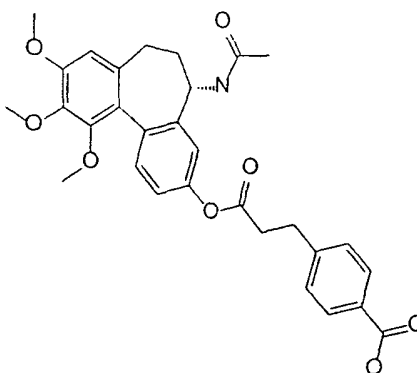
5 8.17 (d, 1H) ; 8.43 (d, 1H).

MS-ESI : 561 [MH]⁺

Elemental analysis	Found	C 66.1	H 6.5	N 4.9
C ₃₂ H ₃₆ N ₂ O ₇ ; 0.3 dichloromethane	Requires	C 66.2	H 6.3	N 4.8%

10 Example 18

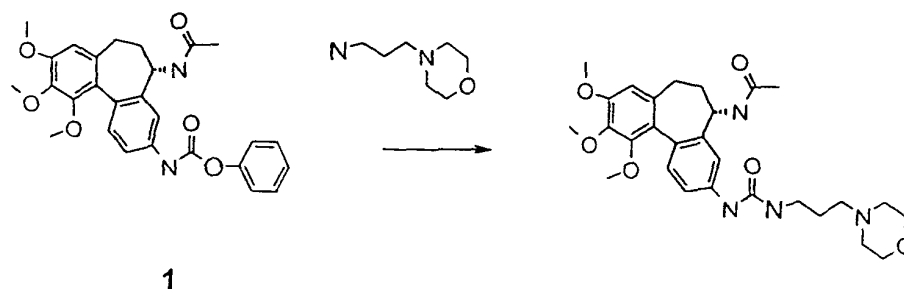
CHIRAL



A solution of *N*-acetyl-colchicicol (0.357 g ; 1 mmol), EDCI (0.23 g ; 1.2 mmol), DMAP (0.025 g ; 0.2 mmol) and 3-(4-carboxyphenyl)propionic acid (0.233 g ; 1.2 mmol) was stirred at ambient temperature overnight. After removal of the solvent by evaporation, the residue was purified by preparative HPLC on reverse phase silica eluting with methanol/ammonium carbonate buffer (2 g/l pH7) (50/50) to give 4-(3-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]oxy-3-oxopropyl)benzoic acid.

20 Yield : 70%

¹H NMR spectrum (DMSO-d₆) : 1.82-1.93 (m, 4H) ; 1.97-2.22 (m, 2H) ; 2.39-2.63 (m, 1H) ; 2.93-2.99 (m, 2H) ; 2.99-3.06 (m, 2H) ; 3.51 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 3.47-3.56 (m, 1H) ; 6.89 (s, 1H) ; 6.94 (d, 1H) ; 6.99 (dd, 1H) ; 7.30-7.37 (m, 3H) ; 7.85 (d, 2H) ; 8.46 (d, 1H).

MS-ESI : 534 [MH]⁺**Example 19**

5

A solution of *N*-[(5*S*)-3-phenoxy-carbonylamino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (1) (0.1 g ; 0.21 mmol) and 4-(3-aminopropyl)morpholine (0.095 g ; 0.66 mmol) in DMSO (1 ml) was stirred at ambient temperature for 1 hour. The mixture was purified by preparative HPLC on reverse phase silica eluting with methanol/ammonium carbonate buffer (2 g/l, pH7) (40/60) to give, after evaporation, *N*-[(5*S*)-9,10,11-trimethoxy-3-((3-morpholinopropyl)amino)carbonylamino]-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide as a foam.

Yield : 84%

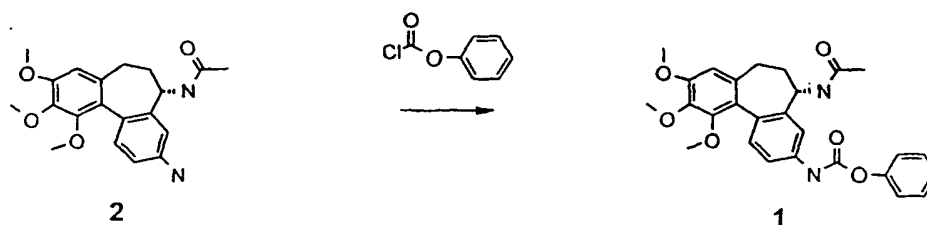
¹H NMR spectrum (DMSO-d₆) : 1.6 (m, 2H) ; 1.88 (s, 3H) ; 1.90 (m, 1H) ; 2.0-2.2 (m, 2H) ; 2.3-2.4 (m, 6H) ; 2.45 (m, 1H, signal obscured by DMSO peak) ; 3.15 (m, 2H) ; 3.47 (s, 3H) ; 3.6 (m, 4H) ; 3.78 (s, 3H) ; 3.83 (d, 3H) ; 4.47 (m, 1H) ; 6.13 (t, 1H) ; 6.76 (s, 1H) ; 7.16 (d, 1H) ; 7.29 (d, 1H) ; 7.37 (dd, 1H) ; 8.37 (d, 1H) ; 8.47 (s, 1H).

MS-ESI : 527 [MH]⁺

Elemental analysis :	Found	C 63.4	H 7.4	N 10.6
C ₂₈ H ₃₈ N ₄ O ₆ ; 0.1 H ₂ O	Requires	C 63.6	H 7.3	N 10.6%

The starting material was prepared as follows:

- 75 -



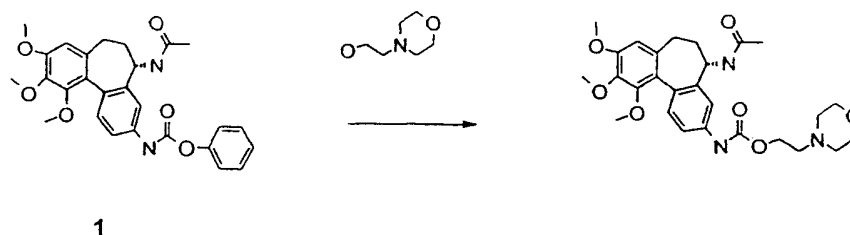
Pyridine (570 μ l ; 7 mmol) and phenyl chloroformate (720 μ l ; 10.3 mmol) were added to a solution of *N*-[(5*S*)-3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-

5 dibenzo[*a,c*]cyclohepten-5-yl]acetamide (2) cooled at 0°C (2 g ; 5.6 mmol) in THF (40 ml), under argon atmosphere. The mixture was stirred at 0°C for 5 minutes and then at ambient temperature for 1 hour. The mixture was extracted with ethyl acetate. The organic phase was washed with 1M hydrochloric acid, saturated sodium hydrogen carbonate and brine. After evaporation to dryness the solid was triturated with ether and hexane to give (1) as a solid.

10 Yield : 89%

¹H NMR spectrum (DMSO-d₆) : 1.82 (s, 3H) ; 1.85 (m, 1H) ; 2.10 (m, 2H) ; 2.5 (m, 1H, signal obscured by DMSO peak) ; 3.47 (s, 3H) ; 3.77 (s, 3H) ; 3.82 (s, 3H) ; 4.48 (m, 1H) ; 6.77 (s, 1H) ; 7.20-7.50 (m, 7H) ; 7.55 (s, 1H) ; 8.38 (d, 1H) ; 9.31 (s, 1H).

15 Example 20



Using an analogous procedure to that described for Example 19, *N*-[(5*S*)-3-phenoxy-carbonylamino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-

20 yl]acetamide (1) was reacted with 4-(2-hydroxyethyl)morpholine and the mixture was heated at 60°C for 2 hours to give *N*-[(5*S*)-3-(2-morpholinoethoxycarbonylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide.

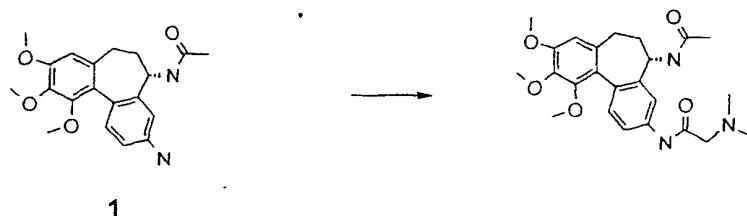
Yield : 84%

¹H NMR spectrum (DMSO-d₆) : 1.89 (s, 3H) ; 1.90 (m, 1H) ; 2.0-2.2 (m, 2H) ; 2.4-2.45 (m, 4H) ; 2.46 (m, 1H, signal obscured by DMSO peak) ; 2.6 (t, 2H) ; 3.42 (s, 3H) ; 3.59 (m, 4H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 4.22 (m, 2H) ; 4.44 (m, 1H) ; 6.78 (s, 1H) ; 7.22 (d, 1H) ; 7.39 (dd, 1H) ; 7.50 (s, 1H) ; 8.39 (d, 1H) ; 9.73 (s, 1H).

5 MS-ESI : 514 [MH]⁺

Elemental analysis :	Found	C 60.4	H 6.6	N 8.0
C ₂₇ H ₃₅ N ₃ O ₇ ; 1.1 H ₂ O	Required	C 60.8	H 7.0	N 7.9%

Example 21



10

A solution of *N*-[(5*S*)-3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (1) (0.2 g ; 0.56 mmol), *N,N*-dimethylglycine (0.058 g ; 0.56 mmol), EDCI (0.14g ; 0.73 mmol) and DMAP (0.014 g ; 0.11 mmol) in

15 dichloromethane (8 ml) was stirred at ambient temperature overnight. The mixture was washed with water and the organic phase was evaporated and purified by preparative HPLC on reverse phase silica eluting with methanol/ammonium carbonate buffer (2 g/l, pH7) (40/60) to give, after evaporation, *N*-[(5*S*)-3-(*N,N*-dimethylaminoacetyl-amino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide as a white foam.

20 Yield : 57%

¹H NMR spectrum (DMSO-d₆) : 1.90 (s, 3H) ; 1.93 (m, 1H) ; 2.0-2.2 (m, 2H) ; 2.31 (s, 6H) ; 2.5 (m, 1H, signal partially obscured by DMSO peak) ; 3.09 (d, 1H) ; 3.10 (d, 1H) ; 3.48 (s, 3H) ; 3.79 (s, 3H) ; 3.84 (s, 3H) ; 4.5 (m, 1H) ; 6.78 (s, 1H) ; 7.25 (d, 1H) ; 7.6 (m, 2H) ; 8.4 (d, 1H) ; 9.73 (s, 1H).

25 MS-ESI : 442 [MH]⁺

Elemental analysis :	Found	C 63.0	H 7.0	N 9.2
C ₂₄ H ₃₁ N ₃ O ₅ ; 0.8 H ₂ O	Required	C 63.2	H 7.2	N 9.2%

Example 22

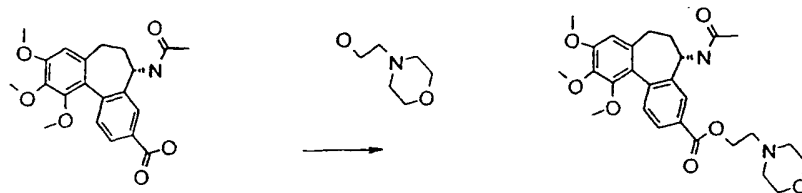
- 5 Using an analogous procedure to that described for Example 21, *N*-[(5*S*)-3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide was reacted with 1-piperidinepropionic acid to give *N*-[(5*S*)-3-(3-piperidinopropionylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide.

Yield : 61%

- 10 ¹H NMR spectrum (DMSO-d₆) : 1.40 (m, 2H) ; 1.55 (m, 4H) ; 1.89 (s, 3H) ; 1.90 (m, 1H) ; 2.0-2.2 (m, 2H) ; 2.4 (br s, 4H) ; 2.45 (m, 2H) ; 2.5 (m, 1H, signal obscured by DMSO peak) ; 2.62 (m, 2H) ; 3.47 (s, 3H) ; 3.79 (s, 3H) ; 3.84 (s, 3H) ; 4.45 (m, 1H) ; 6.78 (s, 1H) ; 7.24 (d, 1H) ; 7.5 (s, 1H) ; 7.58 (dd, 1H) ; 8.40 (d, 1H).

MS-ESI : 496 [MH]⁺

- | | | | | | |
|----|---|----------|--------|-------|--------|
| 15 | Elemental analysis : | Found | C 65.7 | H 7.4 | N 8.2 |
| | C ₂₈ H ₃₇ N ₃ O ₅ | Required | C 65.7 | H 7.6 | N 8.2% |

Example 23

1

20

- A solution of *N*-[(5*S*)-3-carboxy-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (1) (0.385 g ; 1 mmol), EDCI (0.248 g ; 1.3 mmol), DMAP (0.248 g ; 0.2 mmol) and 4-(2-hydroxyethyl)morpholine (127 μl ; 1.05 mmol) was
 25 stirred at ambient temperature overnight. After evaporation to dryness the residue was

purified by preparative HPLC on reverse phase silica eluting with a 40-60% gradient of methanol/ammonium carbonate buffer (2 g/l, pH7) to give, after evaporation, *N*-[(5*S*)-3-(2-morpholinoethoxycarbonyl)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide as a solid.

5 Yield : 47%

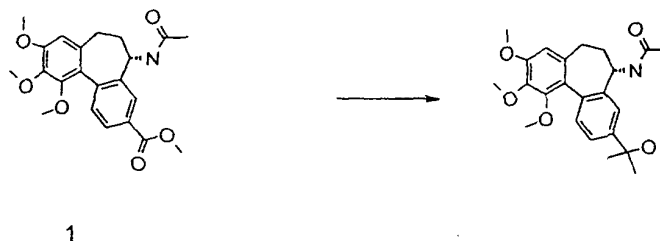
¹H NMR spectrum (DMSO-d₆) : 1.88 (s, 3H) ; 1.88-2.05 (m, 2H) ; 2.2 (m, 1H) ; 2.5 (m, 5H, signal obscured by DMSO peak) ; 2.7 (m, 2H) ; 3.5 (s, 3H) ; 3.6 (m, 4H) ; 3.79 (s, 3H) ; 3.85 (s, 3H) ; 4.4 (m, 2H) ; 4.55 (m, 1H) ; 6.82 (s, 1H) ; 7.47 (d, 1H) ; 7.89 (dd, 1H) ; 7.95 (d, 1H) ; 8.58 (d, 1H).

10 MS-ESI : 499 [MH]⁺

Elemental analysis :	Found	C 63.2	H 6.7	N 5.5
C ₂₇ H ₃₄ N ₂ O ₇ ; 0.6 H ₂ O	Required	C 65.0	H 6.9	N 5.6%

Example 24

15



A solution of methyllithium in ether (1.6 M ; 2.14 ml ; 3.4 mmol) was added at -78°C under argon atmosphere to dry THF (5 ml). After 5 minutes a solution of *N*-[(5*S*)-3-(methoxycarbonyl)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (1) (0.274 g ; 0.68 mmol) in THF (11 ml) was added. The mixture was stirred at -78°C for 30 minutes, allowed to warm up and further stirred at ambient temperature for 90 minutes. After removal of the solvents by evaporation, the residue was taken up in an aqueous ammonium chloride/ethyl acetate mixture and extracted. The organic phase was

20 evaporated and purified by flash chromatography eluting with ethyl acetate to give *N*-[(5*S*)-3-(1-hydroxy-1-methylethyl)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide as a white foam.

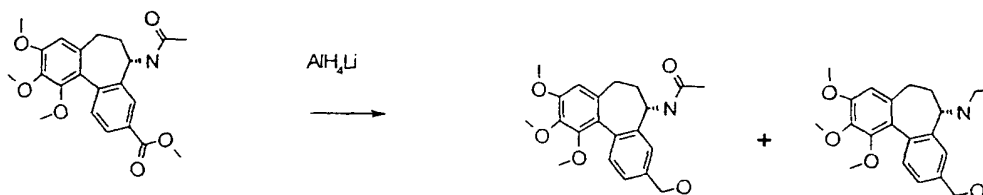
Yield : 45%

¹H NMR spectrum (DMSO-d₆) : 1.45 (s, 3H) ; 1.48 (s, 3H) ; 1.86 (m, 1H) ; 1.88 (s, 3H) ; 2.03 (m, 1H) ; 2.15 (m, 1H) ; 2.5 (m, 1H, signal obscured by DMSO peak) ; 3.5 (s, 3H) ; 3.77 (s, 3H) ; 3.83 (s, 3H) ; 6.77 (s, 1H) ; 7.23 (d, 1H) ; 7.35 (dd, 1H) ; 7.5 (d, 1H) ; 8.43 (d, 1H).

MS-ESI : 422.1 [MNa]⁺

5	Elemental analysis :	Found	C 66.5	H 7.3	N 3.5
	C ₂₃ H ₂₉ NO ₅ ; 0.8 H ₂ O	Required	C 66.7	H 7.5	N 3.4%

Examples 25 and 26



10

A suspension of (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cycloheptene-3-carboxylate (2.28 ml ; 5.7 mmol) and lithium aluminium hydride (0.216 g ; 22.8 mmol) in a mixture of THF (10 ml) and ether (60 ml) was stirred at reflux under argon atmosphere overnight. After addition of water (60 ml), the mixture was stirred for 2 hours. The resulting solid was filtered and the filtrate was evaporated and purified by flash chromatography eluting with a 5-10% gradient of methanol/dichloromethane to give, after evaporation, *N*-[(5*S*)-3-hydroxymethyl-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (yield : 33%) and [(5*S*)-5-(ethylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]methanol (yield : 47%).

20

Example 25

¹H NMR spectrum (DMSO-d₆) : 1.86 (m, 1H) ; 1.87 (s, 3H) ; 2.01 (m, 1H) ; 2.14 (m, 1H) ; 2.48 (m, 1H, signal obscured by DMSO peak) ; 3.46 (s, 3H) ; 3.77 (s, 3H) ; 3.83 (s, 3H) ; 4.54 (m, 3H) ; 5.21 (t, 1H) ; 6.78 (s, 1H) ; 7.27 (m, 2H) ; 7.32 (s, 1H) ; 8.42 (d, 1H).

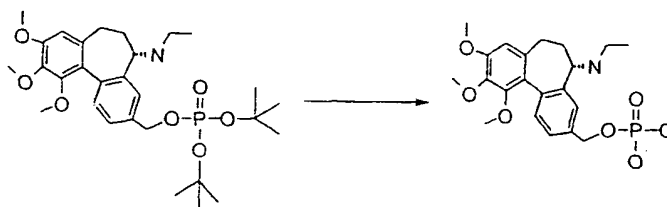
25 MS-ESI : 394.1 [MH]⁺

	Elemental analysis :	Found	C 66.0	H 6.8	N 3.7
	C ₂₁ H ₂₅ NO ₅ ; 0.5 H ₂ O	Requires	C 66.3	H 6.9	N 3.7%

Example 26

¹H NMR spectrum (DMSO-d₆) : 1.90 (s, 3H) ; 1.90 (m, 1H) ; 2.01 (m, 1H) ; 2.20 (m, 1H) ; 2.5 (m, 1H, signal obscured by DMSO peak) ; 3.53 (s, 3H) ; 3.78 (s, 3H) ; 3.85 (s, 3H) ; 4.53 (m, 1H) ; 6.84 (s, 1H) ; 7.50 (d, 1H) ; 7.72 (d, 1H) ; 7.77 (dd, 1H) ; 8.45 (d, 1H).

5 MS-ESI : 389 [MNa]⁺

Example 27

1

A solution of (5*S*)-5-(ethylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-

10 dibenzo[*a,c*]cyclohepten-3-yl di-*tert*-butyl phosphate (1) (0.215 g ; 0.391 mmol) in 1M hydrogen chloride solution in 1,4-dioxane (2 ml) was stirred at ambient temperature overnight. After addition of ether (20 ml) the resulting precipitate was filtered, washed with ether and dried to give (5*S*)-5-(ethylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl dihydrogen phosphate.

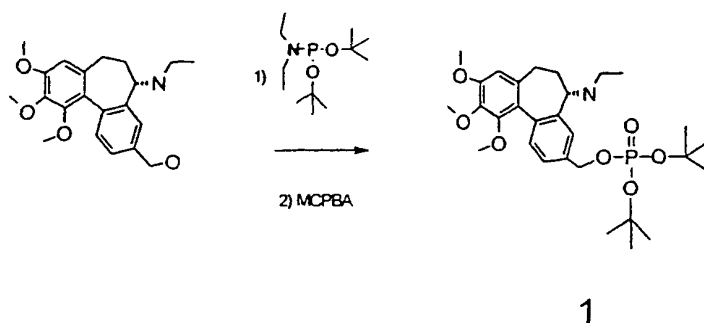
15 Yield : 88%

¹H NMR spectrum (DMSO-d₆) : 1.04 (t, 3H) ; 1.78 (m, 1H) ; 2.0 (m, 1H) ; 2.32 (m, 1H) ; 2.5 (m, 3H, signals obscured by DMSO peak) ; 3.48 (s, 3H) ; 3.5 (m, 1H,) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 4.79 (m, 3H) ; 6.78 (s, 1H) ; 7.27 (s, 2H) ; 7.66 (s, 1H).

MS-ESI : 460 [MH]⁺

20

The starting material was prepared as follows:

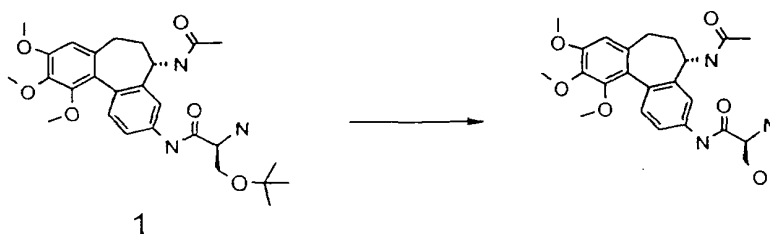


1*H*-Tetrazole (0.182 g ; 2.6 mmol) was added, under argon atmosphere, to a solution of [(5*S*)-5-(ethylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]methanol, (prepared as described in Example 26), (0.3 g ; 0.84 mmol) and di-*tert*-butyl diethylphosphoramidite (0.33 g ; 1.34 mmol) in dry THF (5.5 ml). After 5 minutes, the solution was cooled to -78°C and a solution of *m*-chloroperbenzoic acid (0.375 g ; 1.68 mmol) in dichloromethane (3 ml) was added in portions. The mixture was allowed to warm to ambient temperature and further stirred for 5 minutes. After addition of aqueous ammonium hydrogen carbonate and aqueous sodium sulphite, the organic solvent was removed by evaporation and the residue was taken up in dichloromethane. The organic phase was washed with water, dried and evaporated. The residue was purified by flash chromatography eluting with ethyl acetate/methanol (95/5) to give (1) as a foam.

Yield : 54 %.

¹H NMR spectrum (DMSO-*d*₆) : 1.03 (t, 3H) ; 1.43 (s, 18H) ; 1.72 (m, 1H) ; 2.0 (m, 1H) ; 2.35 (m, 1H) ; 2.50 (m, 3H, signal obscured by DMSO peak) ; 3.2-3.6 (m, 1H signal obscured by H₂O peak) ; 3.50 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 4.99 (m, 2H) ; 6.80 (s, 1H) ; 7.35 (m, 2H).

Example 28



12N Hydrochloric acid (5ml) was added to a solution of (2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]-2-amino-3-*tert*butoxypropanamide (1) (0.35 g ; 0.7 mmol) in 1,4-dioxane (5 ml). The mixture was heated at 60°C under argon atmosphere for 1 hour. After dilution with ether, the resulting precipitate was filtered, washed with ether and dried to give (2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]-2-amino-3-hydroxypropanamide as a white solid.

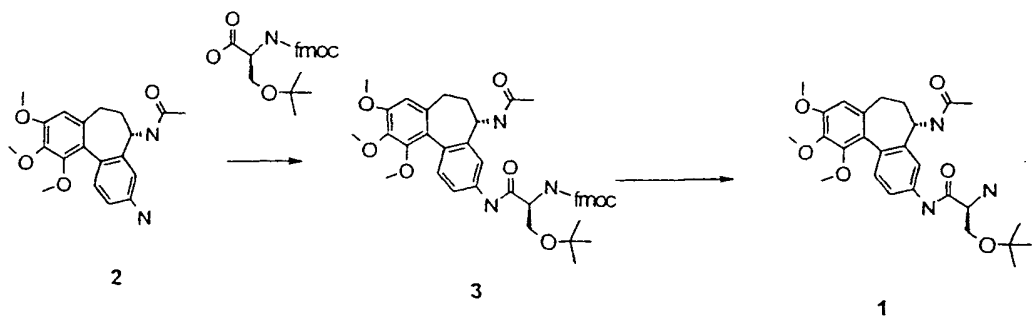
Yield : 65%

¹H NMR spectrum (DMSO-d₆) : 1.90 (s, 3H) ; 1.95 (m, 1H) ; 2.05 (m, 1H) ; 2.18 (m, 1H) ;

2.50 (m, 1H, signal obscured by DMSO peak) ; 3.48 (s, 3H) ; 3.79 (s, 3H) ; 3.84 (s, 3H) ; 3.88 (m, 2H) ; 4.05 (m, 1H) ; 4.45 (m, 1H) ; 6.8 (s, 1H) ; 7.29 (d, 1H) ; 7.58 (d, 1H) ; 7.65 (dd, 1H) ; 8.32 (br s, 3H) ; 8.47 (d, 1H).

MS-ESI : 444 [MH]⁺

The starting material was prepared as follows:



O-(7-(Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.468 g ; 1.28 mmol) and *N*-[(5*S*)-3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-

dibenzo[*a,c*]cyclohepten-5-yl]acetamide (2) (0.398 g ; 1.12 mmol) were added to a solution of *N*-fmoc-*O*-*tert*-butyl-L-serine (0.428 g ; 1.12 mmol) in dichloromethane (18ml) and *N,N*-diisopropylethylamine (0.222 ml ; 1.28 mmol). The mixture was stirred overnight under argon atmosphere at ambient temperature. After addition of water, the organic phase was dried over MgSO₄ and evaporated to give (2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]-2-(fmoc-amino)-3-(*tert*butoxy)propanamide (3).

Yield : 95%

¹H NMR spectrum (DMSO-d₆) : 1.14 (s, 9H) ; 1.87 (s, 3H) ; 1.80 (m, 1H) ; 2.0-2.2 (m, 2H) ; 2.5 (m, 1H, signal obscured by DMSO peak) ; 3.46 (s, 3H) ; 3.50-3.60 (m, 2H) ; 3.77 (s, 3H) ; 3.82 (s, 3H) ; 4.20-4.35 (m, 4H) ; 4.45 (m, 1H) ; 6.77 (s, 1H) ; 7.25 (d, 1H) ; 7.32 (m, 2H) ; 7.42 (m, 2H) ; 7.54 (m, 2H) ; 7.61 (s, 1H) ; 7.76 (m, 2H) ; 7.89 (m, 2H) ; 8.40 (d, 1H).

MS-ESI : 744 [MNa]⁺

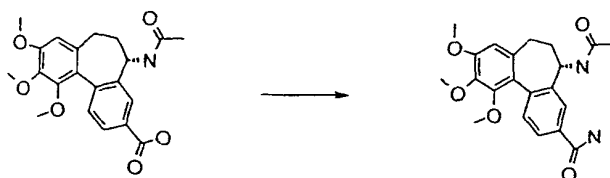
A solution of (3) (0.75 g ; 1.04 mmol) and piperidine (1 ml) in dichloromethane (1.5 ml) was stirred at ambient temperature for 45 minutes. After evaporation to dryness the residue was purified by flash chromatography eluting with ethyl acetate/methanol (95/5) to give (1) as a foam.

Yield : 70%

¹H NMR spectrum (DMSO-d₆) : 1.14 (s, 9H) ; 1.87 (s, 3H) ; 1.89 (m, 1H) ; 1.90-2.15 (m, 2H) ; 2.5 (m, 1H, signal obscured by DMSO peak) ; 3.46 (s, 3H) ; 3.40-3.50 (m, 3H) ; 3.77 (s, 3H) ; 3.82 (s, 3H) ; 4.49 (m, 1H) ; 6.77 (s, 1H) ; 7.25 (d, 1H) ; 7.58 (m, 2H) ; 8.39 (d, 1H).

MS-ESI : 500.2 [MH]⁺

Example 29



Oxalyl chloride (0.44 g ; 3.4 mmol) and DMF (50 μ l) were added to a suspension of *N*-[(5*S*)-3-carboxy-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (1) under argon atmosphere (1.15 g ; 3 mmol) in dichloromethane (10 ml). The mixture was stirred at ambient temperature for 2 hours, evaporated to dryness and redissolved in dichloromethane (20 ml). The solution was cooled at -78° C and ammonia gas was allowed to bubble through the solution for 5 minutes. The mixture was allowed to warm up and further stirred at ambient temperature for 15 minutes. After evaporation to dryness, the residue was taken up in aqueous sodium hydrogen carbonate/ethyl acetate. The organic phase was separated, evaporated and purified by flash chromatography eluting with ethyl

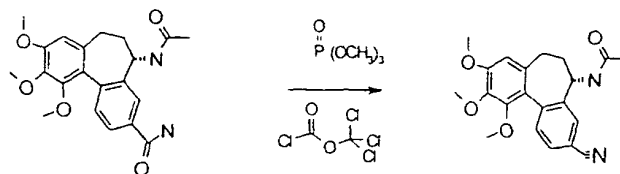
acetate/methanol (95/5) to give *N*-[(5*S*)-3-carbamoyl-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide.

Yield : 20 %

¹H NMR spectrum (DMSO-d₆) : 1.89 (s, 3H) ; 1.89 (m, 1H) ; 1.96 (m, 1H) ; 2.5 (m, 1H, signal obscured by DMSO peak) ; 3.49 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 4.54 (m, 1H) ; 6.81 (s, 1H) ; 7.36 (d, 1H) ; 7.78 (dd, 1H) ; 7.87 (d, 1H) ; 7.96 (s, 1H) ; 8.47 (d, 1H).

MS-ESI : 407 [MNa]⁺

Example 30



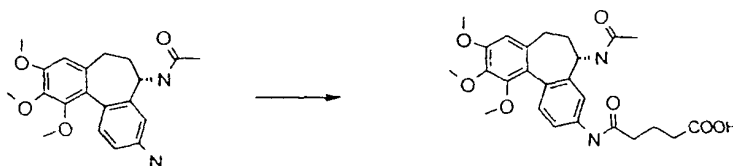
Trichloromethyl chloroformate (0.094 ml ; 0.77 mmol) was added in portions at 0°C to a solution of *N*-[(5*S*)-3-carbamoyl-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (0.2 g ; 0.484 mmol), (prepared as described for Example 29) and trimethyl phosphate (0.306 ml ; 2.6 mmol). The mixture was allowed to warm up and then heated at 60°C for 5 minutes. The reaction mixture was poured onto ice and stirred. The resulting precipitate was filtered, dried and purified by flash chromatography, eluting with dichloromethane/ethyl acetate (1/1) to give *N*-[(5*S*)-3-cyano-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide.

Yield : 61 %.

¹H NMR spectrum (DMSO-d₆) : 0.97 (t, 3H) ; 1.60 (m, 1H) ; 1.95 (m, 2H) ; 2.30 (m, 2H) ; 2.45 (m, 1H, signal partially obscured by DMSO peak) ; 3.46 (s, 3H) ; 3.76 (s, 3H) ; 3.82 (s, 3H) ; 4.54 (m, 2H) ; 5.16 (t, 1H) ; 6.75 (s, 1H) ; 7.15-7.30 (m, 2H) ; 7.53 (s, 1H).

MS-ESI : 358 [MH]⁺

Example 31



A solution of *N*-[(5*S*)-3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (1) (0.3 g ; 84 mmol) and glutaric anhydride (0.199 g ; 84 mmol) in dichloromethane (20 ml) was stirred at ambient temperature for 90 minutes.

- 5 After removal of the solvent by evaporation, the residue was purified by flash chromatography, eluting with dichloromethane /methanol (80/20) to give, after trituration in ether, *N*-[(5*S*)-3-(4-carboxybutanoylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide as a white solid.

Yield : 63 %

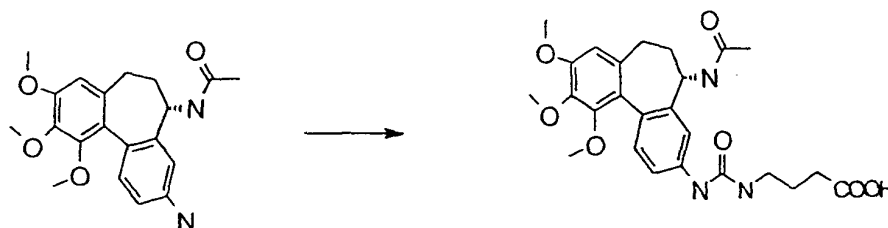
- 10 ¹H NMR spectrum (DMSO-d₆) : 1.8-2 (m, 3H) ; 1.88 (s, 3H) ; 2-2.25 (m, 2H) ; 2.26 (t, 2H) ; 2.36 (t, 2H) ; 2.5 (s, 1H, signal partially observed by DMSO peak) ; 3.46 (s, 3H) ; 3.77 (s, 3H) ; 3.82 (s, 3H) ; 4.48 (m, 1H) ; 6.76 (s, 1H) ; 7.22 (d, 1H) ; 7.53 (d, 1H) ; 7.56 (s, 1H) ; 8.4 (d, 1H) ; 9.97 (s, 1H).

MS-ESI / 471 [MH]⁺

- | | | | | | |
|----|---|----------|--------|-------|--------|
| 15 | Elemental analysis | Found | C 59.2 | H 6.2 | N 5.4 |
| | C ₂₅ H ₃₀ N ₂ O ₇ | Requires | C 63.8 | H 6.4 | N 6.0% |

Example 32

20



- A suspension of 4-aminobutyric acid (0.111 g ; 1.08 mmol) and *N,O*-bis(trimethylsilyl)acetamide (1.8 ml ; 7.3 mmol) in dichloromethane (10 ml) was stirred at ambient temperature for 2 hours. The mixture was evaporated to dryness and redissolved in dichloromethane (10 ml) under argon atmosphere. A solution of *N*-[(5*S*)-3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (0.35 g ; 0.98 mmol), phenyl chloroformate (135 μl ; 1.08 mmol) and triethylamine (151 μl ; 1.08 mmol) in

dichloromethane (10 ml) was stirred for 1 hour under argon atmosphere and added to the above solution. The mixture was stirred overnight, evaporated and purified by preparative HPLC on reverse phase silica eluting with a 0-30 % gradient of methanol/ammonium carbonate buffer pH7 to give, after evaporation, 4-[(*5S*)-5-(acetylamino)-9,10,11-

5 trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]aminocarbonyl]amino]butanoic acid as a solid

Yield : 50 %

¹H NMR spectrum (DMSO-d₆, CF₃CO₂D) : 1.68 (m, 2H) ; 1.88 (s, 3H) ; 1.85-2 (m, 1H) ; 2-2.2 (m, 2H) ; 2.27 (m, 2H) ; 2.5 (m, 1H, signal partially observed by DMSO peak) ; 3.12 (m, 2H) ; 3.47 (s, 3H) ; 3.78 (s, 3H) ; 3.83 (s, 3H) ; 4.48 (m, 1H) ; 6.75 (s, 1H) ; 7.17 (d, 1H) ; 7.3 (s, 1H) ; 7.39 (d, 1H).

MS-ESI : 486 [MH]⁺

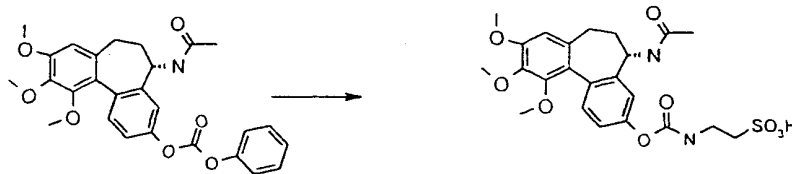
Elemental analysis

Found C 58.3 H 6.5 N 8.7

C₂₅H₃₁N₃O₇

Requires C 61.8 H 6.4 N 8.7%

Example 33



1

A solution of *N*-[(*5S*)-3-phenoxy-carbonyloxy-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (1) (0.35 g ; 0.73 mmol), 2-aminomethanesulphonic acid (0.156 g ; 1.25 mmol) and triethylamine (174 μl ; 1.25 mmol) in DMSO (2.5 ml) was heated at 70°C for 2 days. The mixture was taken up in water and purified by preparative HPLC eluting with a 0-30 % gradient of methanol/ammonium carbonate buffer (2 g/l pH7). The appropriate fractions were evaporated and the resulting solid triturated in ether and dried

to give 2-[[[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]oxycarbonyl]amino]ethane-1-sulphonic acid.

Yield : 22 %

¹H NMR spectrum (DMSO-d₆ ; CF₃CO₂D) : 1.89 (s, 3H) ; 1.8-1.95 (m, 1H) ; 2-2.5 (m, 2H) ;

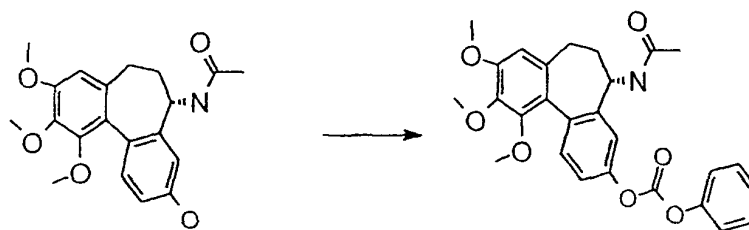
5 2.5 (m, 1H, signal partially obscured by DMSO peak) ; 2.71 (t, 2H) ; 3.4 (m, 2H) ; 3.54 (s, 3H) ; 3.8 (s, 3H) ; 3.85 (s, 3H) ; 4.58 (m, 1H) ; 6.8 (s, 1H) ; 7.08 (d, 1H) ; 7.1 (s, 1H) ; 7.32 (d, 1H).

MS-ESI : 509 [MH]⁺

Elemental analysis: Found C 48.1 H 6.0 N 7.3 S 5.2

10 C₂₃H₂₈N₂O₉S ; 1 NH₃, 2.5 H₂O Requires C 48.4 H 6.4 N 7.4 S 5.6%

The starting material was prepared as follows:



15

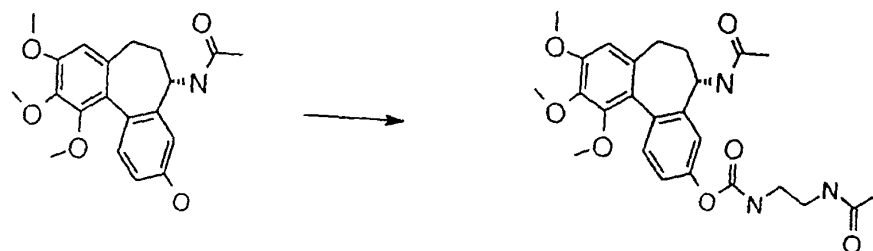
A solution of *N*-acetyl colchicinol (0.35 g ; 0.98 mmol), phenyl chloroformate (145 μl ; 1.08 mmol) and triethylamine (150 μl ; 1.08 mmol) in dichloromethane (20 ml) was stirred at ambient temperature for 1 hour. The mixture was washed with water and the organic phase evaporated. The residue was purified by flash chromatography, eluting with ethyl

20 acetate/petroleum ether (80/20) to give *N*-[(5*S*)-3-phenoxy-carbonyloxy-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide as a foam.

Yield : 79 %

¹H NMR spectrum (DMSO-d₆) : 1.89 (s, 3H) ; 1.8-1.95 (m, 1H) ; 2-2.3 (m, 2H) ; 2.5 (m, 1H, signal partially obscured by DMSO peak) ; 3.52 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 4.58 (m,

25 1H) ; 6.8 (s, 1H) ; 7.2 - 7.6 (m, 8H) ; 8.41 (d, 1H).

Example 34

- 5 A solution of *N*-acetyl-cochicinol (0.25 g ; 0.7 mmol), 4-nitrophenyl chloroformate (0.169 g ; 0.84 mmol) and triethylamine (117 μ l ; 0.84 mmol) in dichloromethane (10 ml) was stirred under argon atmosphere for 1 hour. *N*-Acetylenethylenediamine (0.086 g ; 0.84 mmol) was then added and the mixture was stirred further for 3 hours. After evaporation to dryness, the residue was purified by flash chromatography, eluting with
- 10 methanol/acetonitrile/dichloromethane (4/48/48) to give (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl *N*-[2-(acetylamino)ethyl]carbamate.

Yield : 49 %

- ¹H NMR spectrum (DMSO-*d*₆) : 1.84 (s, 3H) ; 1.88 (s, 3H) ; 1.85-1.95 (m, 1H) ; 2-2.25 (m, 2H) ; 2.5 (m, 1H, signal partially observed by H₂O peak) ; 3.53 (s, 3H) ; 3.79 (s, 3H) ; 3.85 (s, 3H) ; 4.55 (m, 1H) ; 6.81 (s, 1H) ; 7.06 (dd, 1H) ; 7.07 (d, 1H) ; 7.32 (d, 1H) ; 7.79 (m, 1H) ; 7.8 (m, 1H) ; 8.41 (d, 1H).
- 15

MS-ESI : 486.1 [MH]⁺

Elemental analysis

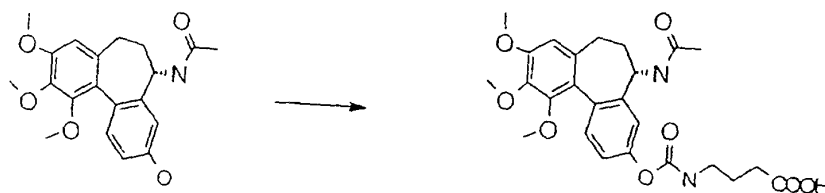
20 C₂₅H₃₁N₃O₇ 0.6 H₂O

Found

C 60.3 H 6.6 N 8.3

Requires

C 60.5 H 6.5 N 8.5%

Example 35

A suspension of 4-aminobutyric acid (0.087 g ; 0.84 mmol) and *N,O*-bis(trimethylsilyl)acetamide (0.865 ml ; 3.5 mmol) in dichloromethane (10 ml) was stirred under argon atmosphere for 3 hours and evaporated to dryness. The residue was then
 5 redissolved in dichloromethane (10 ml). 4-Nitrophenyl chloroformate (0.17 g ; 0.84 mmol) and triethylamine (0.117 ml ; 0.84 mmol) were added to a solution of *N*-acetyl-colchicicol (0.25 g ; 0.7 mmol) in dichloromethane (10 ml). The solution was stirred for 1 hour and added to the above solution. The resulting mixture was stirred further for 3 hours. After evaporation to dryness the residue was purified by preparative HPLC on reverse phase silica
 10 eluting with methanol/ammonium carbonate buffer (2 g/l pH7) (30/70) to give, after evaporation of the appropriate fractions, 4-[[[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]oxycarbonyl]amino]butanoic acid.

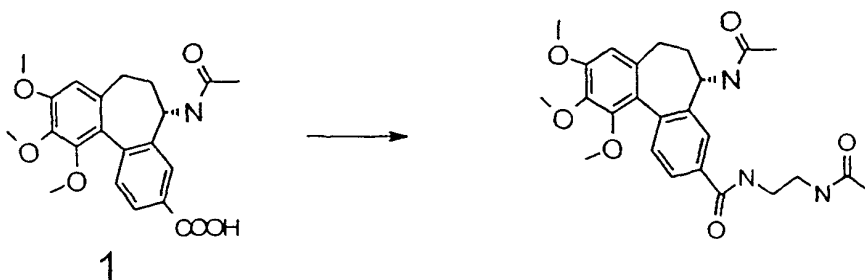
Yield : 44 %

¹H NMR spectrum (DMSO-d₆, CF₃CO₂D) : 1.73 (m, 2H) ; 1.88 (s, 3H) ; 1.8-1.95 (m, 1H) ; 2-
 15 2.25 (m, 2H) ; 2.3 (m, 2H) ; 2.5 (m, 1H, signal partially obscured by DMSO peak) ; 3.11 (m, 2H) ; 3.53 (s, 3H) ; 3.79 (s, 3H) ; 3.84 (s, 3H) ; 4.45 (m, 1H) ; 6.8 (s, 1H) ; 7.05 (dd, 1H) ; 7.07 (d, 1H) ; 7.31 (d, 1H) ; 7.87 (m, 1H) ; 8.42 (d, 1H).

MS-ESI : 487.1 [MH]⁺

Elemental analysis	Found	C 60.2	H 6.3	N 6.0
20 C ₂₅ H ₃₀ N ₂ O ₈ · 0.5 H ₂ O	Requires	C 60.6	H 6.3	N 5.7%

Example 36



25 A mixture of *N*-[(5*S*)-3-carboxy-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (1) (0.3 g ; 0.78 mmol), DCCl (0.193 g ; 0.93 mmol),

DMAP (0.019 g ; 0.15 mmol) and *N*-acetyllethylenediamine (0.096 g ; 0.985 mmol) in dichloromethane was stirred at ambient temperature overnight. After evaporation of the solvent, the residue was purified by flash chromatography and eluted with

5 **9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide.**

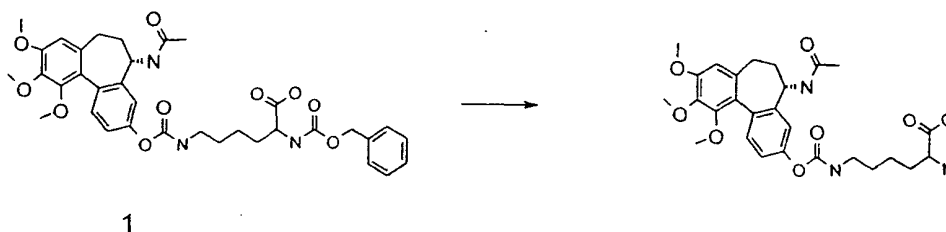
Yield : 71 %

¹H NMR spectrum (DMSO-d₆) : 1.82 (s, 3H) ; 1.89 (s, 3H) ; 1.85-2.05 (m, 2H) ; 2.17 (m, 1H) ; 2.5 (m, 1H, signal partially obscured by DMSO peak) ; 3.22 (m, 2H) ; 3.32 (m, 2H, signal partially observed by H₂O peak) ; 3.49 (s, 3H) ; 3.79 (s, 3H) ; 3.84 (s, 3H) ; 4.55 (m, 1H) ;
10 6.81 (s, 1H) ; 7.38 (d, 1H) ; 7.75 (dd, 1H) ; 7.84 (d, 1H) ; 8 (m, 1H) ; 8.52 (m, 2H).

MS-ESI : 470.2 [MH]⁺

Elemental analysis:	Found	C 60.3	H 6.6	N 8.2
C ₂₃ H ₃₁ N ₃ O ₆ 0.4 dichloromethane	Requires	C 60.6	H 6.4	N 8.4%

15 **Example 37**



A solution of 6-[[[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-
20 dibenzo[*a,c*]cyclohepten-3-yl]oxy}carbonyl)amino]-2-(benzyloxycarbonylamino)-hexanoic
acid (1) (0.4 g ; 0.6 mmol) in ethanol (80 ml) was hydrogenated in the presence of 10%
palladium on carbon (0.08 g). After filtration of the catalyst and evaporation to dryness, the
residue was purified by preparative HPLC eluting with a 0-40% gradient of
methanol/ammonium carbonate buffer (2 g/l pH7) to give, after evaporation and trituration in
25 ether, 6-[[[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-
dibenzo[*a,c*]cyclohepten-3-yl]oxy}carbonyl)amino]-2-aminohexanoic acid as a solid.

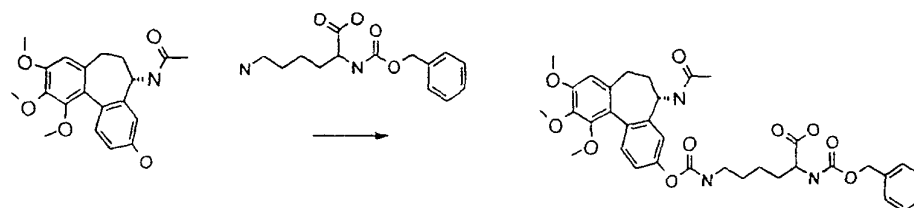
Yield : 75 %

¹H NMR spectrum (DMSO-d₆) : 1.35-1.55 -m, 4H) ; 1.62 (m, 1H) ; 1.72 (m, 1H) ; 1.9 (s, 3H) ; 1.9 (m, 1H) ; 2.05 (m, 1H) ; 2.15 (m, 1H) ; 2.5 (m, 1H, signal partially obscured by DMSO peak) ; 3-3.2 (m, 3H) ; 3.51 (s, 3H) ; 3.78 (s, 3H) ; 3.83 (s, 3H) ; 4.55 (m, 1H) ; 6.79 (s, 1H) ; 7.02 (dd, 1H) ; 7.12 (d, 1H) ; 7.29 (d, 1H) ; 7.74 (m, 1H) ; 8.7 (d, 1H).

5 MS-ESI : 530.1 [MH]⁺

Elemental analysis:	Found	C 60.2	H 7.0	N 7.8
C ₂₇ H ₃₅ N ₃ O ₉ 0.5 H ₂ O	Requires	C 60.2	H 6.7	N 7.8%

The starting material was prepared as follows:



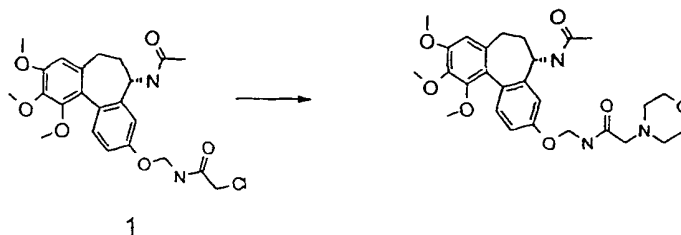
1

10

A suspension of *N*-(carboxybenzyloxy)-L-lysine (0.141 g ; 0.5 mmol) and *N,O*-bis(trimethylsilyl)acetamide (0.519 ml ; 2 mmol) in dichloromethane (10 ml) was stirred at ambient temperature under argon atmosphere for 3 hours. The mixture was evaporated to dryness and the residue redissolved in dichloromethane (10 ml). A solution of *N*-acetyl-
 15 colchicinol (0.15 g ; 0.42 mmol), and 4-nitrophenyl chloroformate (0.102g; 0.5mmol) was stirred at ambient temperature for 1 hour and then added to the above solution. The resulting mixture was stirred overnight, evaporated to dryness and purified by preparative HPLC eluting with a 0-55% gradient of methanol/ammonium carbonate buffer (2 g/l pH7) to give (1).

20 Yield : 63 %

¹H NMR spectrum (DMSO-d₆) : 1.35 (m, 2H) ; 1.49 (m, 2H) ; 1.62 (m, 1H) ; 1.72 (m, 1H) ; 1.89 (s, 3H) ; 1.9 (m, 1H) ; 2.07 (m, 1H) ; 2.15 (m, 1H) ; 2.5 (m, 1H, signal partially obscured by DMSO peak) ; 3.07 (m, 2H) ; 3.52 (s, 3H) ; 3.8 (s, 3H) ; 3.85 (s, 3H) ; 4.57 (m, 1H) ; 5.05 (m, 2H) ; 6.81 (s, 1H) ; 7 (m, 1H) ; 7.05 (dd, 1H) ; 7.1 (d, 1H) ; 7.32 (d, 1H) ; 7.3-7.4 (m, 5H)
 25 ; 7.75 (m, 1H) ; 8.58 (d, 1H).

Example 38

5

A solution of *N*-([(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]oxymethyl)-2-chloroacetamide (1) (0.25 g ; 0.55 mmol) in morpholine (2 ml) was stirred at ambient temperature for 2 hours. After addition of dichloromethane and removal of the insoluble material by filtration, the filtrate was

10 evaporated to dryness and the residue was purified by preparative HPLC eluting with a 0-45% gradient of ethanol/ammonium carbonate buffer (2 g/l pH7) to give, after evaporation and trituration in ether, *N*-([(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]oxymethyl)-2-morpholinoacetamide.

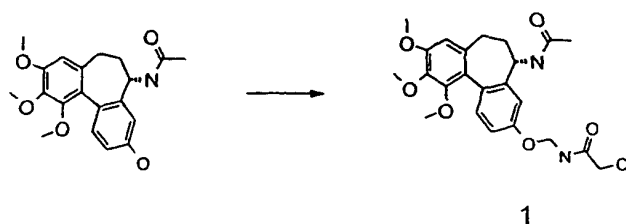
Yield : 60 %

15 ¹H NMR spectrum (DMSO-d₆) : 1.85 (m, 1H) ; 1.88 (s, 3H) ; 1.95-2.2 (m, 2H) ; 2.4 (m, 4H) ; 2.5 (m, 1H, signal partially observed by DMSO peak) ; 3 (s, 2H) ; 3.47 (s, 3H) ; 3.57 (m, 4H) ; 3.77 (s, 3H) ; 3.82 (s, 3H) ; 4.5 (m, 1H) ; 5.18 (m, 2H) ; 6.76 (s, 1H) ; 6.91 (d, 1H) ; 6.98 (dd, 1H) ; 7.22 (d, 1H) ; 8.32 (m, 1H) ; 8.85 (m, 1H).

MS-ESI : 514.1 [MH]⁺

20	Elemental analysis	Found	C 61.2	H 6.9	N 7.9
	C ₂₇ H ₃₅ N ₃ O ₇	Requires	C 61.4	H 7.0	N 8.0%

The starting material was prepared as follows:

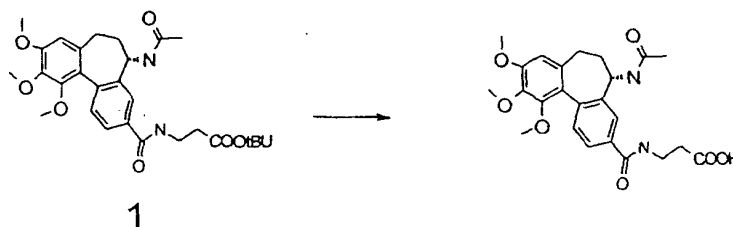


2-Chloro-*N*-(hydroxymethyl)-acetamide (0.342 g ; 2.7 mmol), triphenylphosphine (1.1 g ; 4.19 mmol) and DEAD (0.6 ml ; 4.19 mmol) were added to a solution of *N*-acetylcolchicine (0.3 g ; 0.84 mmol) in dichloromethane (20 ml) under argon atmosphere. The mixture was stirred at ambient temperature for 2 hours, evaporated and purified by flash chromatography eluting with ethyl acetate/dichloromethane (50/50) and dichloromethane/methanol (98/2) to give (1).

Yield : 76 %

10 MS-ESI : 485.1 [MH]⁺

Example 39



15 *N*-[(5*S*)-3-(2-*tert*Butoxycarbonyl)ethylcarbonyl]-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (1) (0.26 g ; 0.5 mmol) in solution in dichloromethane (10 ml) was treated with TFA (10 ml) at ambient temperature for 1 hour. After evaporation to dryness, the residue was purified by preparative HPLC eluting with methanol/ammonium carbonate buffer (2 g/l pH7) (35/65) to give, after evaporation and
20 trituration in ether, 3-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-ylcarbonylamino]propanoic acid as a white solid.

Yield : 56%

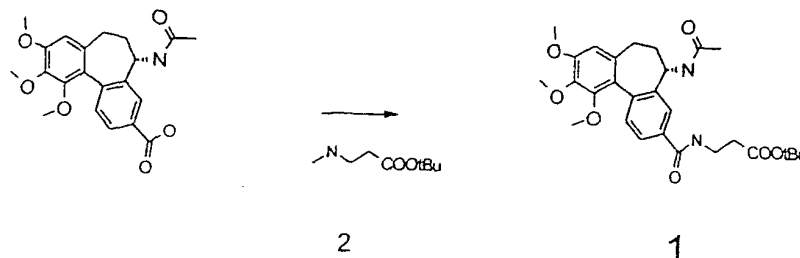
¹H NMR spectrum (DMSO-d₆) : 1.91 (s, 3H) ; 1.85-2.1 (m, 2H) ; 2.2 (m, 1H) ; 2.5 (m, 1H, signal partially observed by DMSO peak) ; 3.2-3.6 (m, 4H, signal partially obscured by H₂O

peak) ; 3.5 (s, 3H) ; 3.8 (s, 3H) ; 3.86 (s, 3H) ; 4.6 (m, 1H) ; 6.82 (s, 1H) ; 7.39 (d, 1H) ; 7.74 (dd, 1H) ; 7.85 (d, 1H) ; 8.54 (d, 1H) ; 8.62 (m, 1H).

MS-ESI : 457.1 [MH]⁺

Elemental analysis:	Found	C 60.9	H 6.7	N 6.7
5 C ₂₄ H ₂₈ N ₂ O ₇	Requires	C 63.2	H 6.2	N 6.1%

The starting material was prepared as follows:



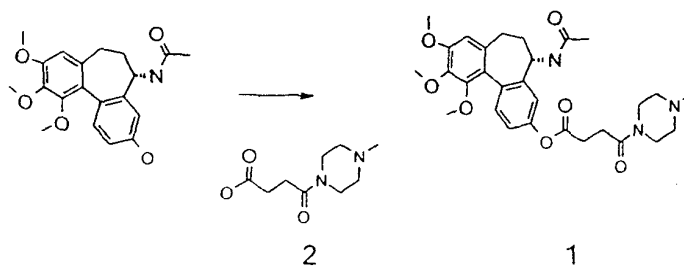
A mixture of *N*-[(5*S*)-3-carboxy-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (1) (0.3 g ; 0.78 mmol), EDCI (0.179 g ; 0.93 mmol), DMAP (0.019 g ; 0.15 mmol), triethylamine (0.13 ml ; 0.985 mmol) and *tert*butyl 3-methylaminopropanoate (0.17 g ; 0.985 mmol) in dichloromethane was stirred at ambient temperature overnight. After removal of the solvent by evaporation, the residue was purified by flash chromatography and eluted with ethyl acetate to give (1).

15 Yield : 84%

¹H NMR spectrum (DMSO-d₆) : 1.4 (s, 9H) ; 1.89 (s, 3H) ; 1.9 (m, 1H) ; 2 (m, 1H) ; 2.17 (m, 1H) ; 2.5 (m, 1H, signal partially obscured by DMSO peak) ; 3.25-3.55 (m, 4H) ; 3.49 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 4.55 (m, 1H) ; 6.81 (s, 1H) ; 7.37 (d, 1H) ; 7.7 (dd, 1H) ; 7.81 (d, 1H) ; 8.5 (m, 2H).

20

Example 40



A suspension of 3-(4-methylpiperazin-1-ylcarbonyl)propanoic acid (2) (0.219 g ; 1.1 mmol), DCCI (0.226 ml ; 1.1 mmol) and DMAP (0.052 ml ; 0.42 mmol) in dichloromethane (20 ml) was stirred under argon atmosphere for 1 hour. *N*-Acetyl-colchicinol (0.3 g ; 0.84 mmol) was then added and the mixture was stirred overnight. After removal of the insoluble material by filtration, the filtrate was evaporated and purified by preparative HPLC eluting with a 0-50% gradient of methanol/ammonium carbonate buffer (2 g/l pH7) to give (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-[4-methylpiperazin-1-ylcarbonyl]propanoate.

Yield : 48 %

¹H NMR spectrum (DMSO-d₆) : 1.80-1.96 (m, 1H) ; 1.88 (s, 3H) ; 2.07 (m, 1H) ; 2.18 (m, 1H) ; 2.20 (s, 3H) ; 2.26 (m, 2H) ; 2.33 (m, 2H) ; 2.59 (m, 1H, signal partially obscured by DMSO peak) ; 2.73 (m, 2H) ; 2.79 (m, 2H) ; 3.48 (m, 4H) ; 3.53 (s, 3H) ; 3.80 (s, 3H) ; 3.86 (s, 3H) ; 4.55 (m, 1H) ; 6.82 (s, 1H) ; 7.03-7.12 (m, 2H) ; 7.36 (d, 1H) ; 8.43 (d, 1H).

MS-ESI : 540 [MH]⁺

15	Elemental analysis	Found	C 63.9	H 7.1	N 7.5
	C ₂₉ H ₃₇ N ₃ O ₇ ; 0.3 H ₂ O	Requires	C 63.9	H 7.0	N 7.7%

The starting material was prepared as follows:

A suspension of *N*-methylpiperazine (1.1 ml ; 10 mmol) and succinic anhydride (1.2 g ; 12 mmol) in dichloromethane (20 ml) was stirred under argon atmosphere for 24 hours.

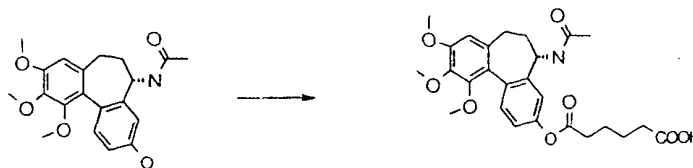
After evaporation to dryness, the residue was triturated in ether/pentane to give (2) as a solid.

Yield : 91 %

¹H NMR Spectrum (DMSO-d₆) : 2.37 (s, 3H) ; 2.53 (m, 2H) ; 2.58 (m, 2H) ; 2.64 (m, 4H) ; 3.59 (m, 2H) ; 3.69 (m, 2H) ; 5.70 (br s, 1H).

25

Example 41



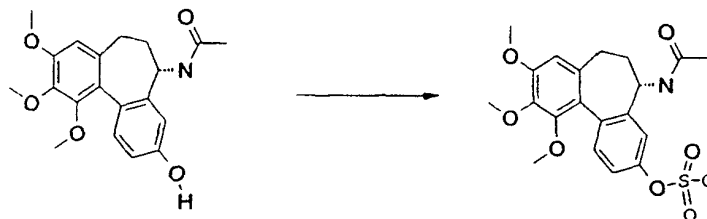
N-Acetyl-colchicinol (0.3 g ; 0.84 mmol) was added under argon atmosphere to a solution of adipic acid (0.147 g ; 1 mmol, *O*-(7-(azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.383 g ; 1 mmol) and diisopropylethylamine (0.352 ml ; 2 mmol) in acetonitrile (20 ml). The reaction mixture was stirred at ambient temperature overnight and evaporated to dryness. The residue was taken up in water (4 ml), the pH was adjusted to 6.5 with 0.1M hydrochloric acid. The solution was purified by preparative HPLC eluting with a 0-40% gradient of methanol/ammonium carbonate buffer (2 g/l pH7) to give 5-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]oxycarbonyl]pentanoic acid.

Yield : 31 %

¹H NMR spectrum (DMSO-d₆) : 1.54-1.75 (m, 4H) ; 1.85-1.90 (m, 1H) ; 1.87 (s, 3H) ; 1.98-2.28 (m, 4H) ; 2.57 (m, 1H, signal partially obscured by DMSO peak) ; 2.61 (t, 2H) ; 3.51 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 4.55 (m, 1H) ; 6.80 (s, 1H) ; 7.04-7.11 (m, 2H) ; 7.34 (d, 1H) ; 8.43 (d, 1H).

MS-ESI : 508 [MNa]⁺

Example 42



Chlorosulphonic acid (1 ml) was added at 0°C in portions to a solution of pyridine (10 ml). After 15 minutes at 0°C, a solution of *N*-acetyl-colchicinol (1 g, 2.8 mmol) in pyridine (10 ml) was added. The solution was stirred overnight at ambient temperature. Water (30 ml) was added and the mixture was adjusted to pH8 by addition of sodium hydrogen carbonate. The aqueous layer was extracted with ether (3 x 20 ml) and purified on HP20SS resin, eluted with a 0-40 % gradient of methanol/water. The volatiles were removed by evaporation to give (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl hydrogen sulphate as a white solid.

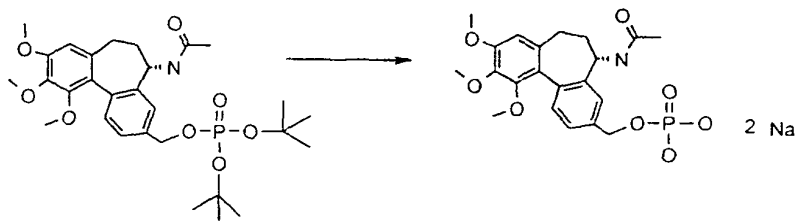
Yield = 71 %

^1H NMR spectrum (DMSO-d_6) : 1.9 (s, 3H), 2-2.2 (m, 2H), 2.5 (m, 1H, signal obscured by DMSO peak), 3.5 (s, 3H), 3.77 (s, 3H), 3.83 (s, 3H), 4.5 (m, 1H), 6.77 (s, 1H), 7.1 (s, 1H), 7.2 (2s, 2H), 8.4 (d, 1H).

MS-ESI : 482 $[\text{M Na}]^+$

5	Elemental analysis:	Found	C 48.1	H 4.9	N 2.8	S 6.2
	$\text{C}_{20}\text{H}_{22}\text{O}_8\text{NSNa}, 2 \text{H}_2\text{O}$	Requires	C 48.5	H 5.3	N 2.8	S 6.5%

Example 43



10

Using an analogous procedure to that described for Example 27 [(5*S*)-5-(acetamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]methyl di-*tert*-butyl phosphate was treated with 1M hydrogen chloride in 1,4-dioxane to give [(5*S*)-5-(acetamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]methyl dihydrogen phosphate.

15

Yield : 95 %

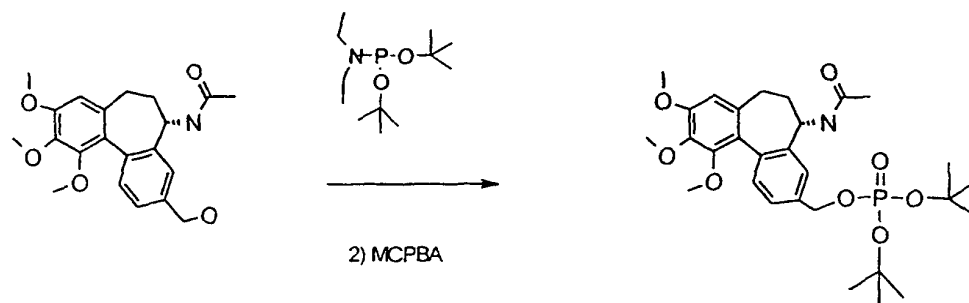
The sodium salt was prepared by addition of 2N sodium hydroxide to a suspension of [(5*S*)-5-(acetamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]methyl dihydrogen phosphate in water until the mixture was at pH7. After freeze-drying, the sodium salt was obtained as a white solid.

20

^1H NMR Spectrum (D_2O) : 1.94 (m, 1H) ; 1.98 (s, 3H) ; 2.15 (m, 1H) ; 2.25 (m, 1H) ; 2.50 (m, 1H) ; 3.50 (s, 3H) ; 3.80 (s, 3H) ; 3.84 (s, 3H) ; 4.48 (m, 1H) ; 4.80 (m, 2H) ; 6.80 (s, 1H) ; 7.40 (m, 3H).

25 MS - ESI : 496 $[\text{MH}]^+$

The starting material was prepared as follows:



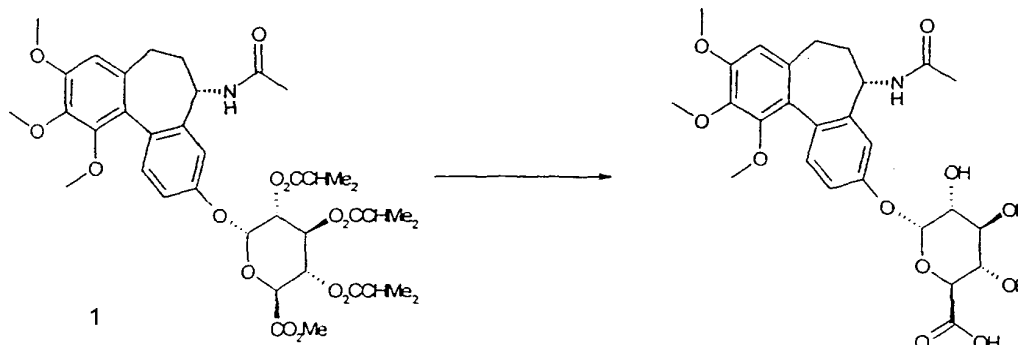
Using an analogous procedure to that described for the starting material in Example 27, *N*-[(5*S*)-3-hydroxymethyl-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide, (prepared as described in Example 25), was reacted with di-*tert*-butyl diethylphosphoramidite to give [(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]methyl di-*tert*-butyl phosphate.

Yield : 59 %

¹H NMR spectrum (DMSO-*d*₆) : 1.432 (s, 9H) ; 1.435 (s, 9H) ; 1.88 (s, 3H) ; 1.90 (m, 1H) ;
 10 2.02 (m, 1H) ; 2.18 (m, 1H) ; 2.5 (m, 1H, signal obscured by DMSO peak) ; 3.50 (s, 3H) ;
 3.79 (s, 3H) ; 3.85 (s, 3H) ; 4.56 (m, 1H) ; 4.97 (d, 2H) ; 6.81 (s, 1H) ; 7.35 (m, 2H) ; 7.38 (s,
 1H) ; 8.46 (d, 1H).

Example 44

15



A solution of methyl (2*S*,3*R*,4*S*,5*R*,6*R*)-6-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]oxy-3,4,5-tris(isobutyryloxy)tetrahydro-2*H*-
 20 pyran-2-carboxylate (1) (515 mg ; 0.68 mol) in methanol (10 ml) and water (1 ml) was treated with lithium hydroxide monohydrate (214 mg ; 5.1 mmol). The reaction mixture was stirred

at ambient temperature and additional solution of lithium hydroxide monohydrate (86 mg ; 2 mmol) in H₂O (1 ml) was added after 12 hours and then again after a further 10 hours to complete the reaction. After a total of 30 hours at ambient temperature, the methanol was removed and the remaining solution was adjusted to pH6 with 2N hydrochloric acid. The resulting heterogeneous solution was deposited on a column of HP20 SS resin (35 ml) for purification, eluting with a 0 to 75 % aqueous solution of methanol. After removal of the solvents by evaporation, the solid was purified further by preparative HPLC on reverse phase silica eluting with a 0-50 % gradient of methanol/water to give, after removal of the methanol by evaporation and freeze drying, (2*S*,3*S*,4*S*,5*R*,6*R*)-6-{[(5*S*)-5-(acetyl-amino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]oxy}-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-carboxylic acid as a white solid (260 mg).

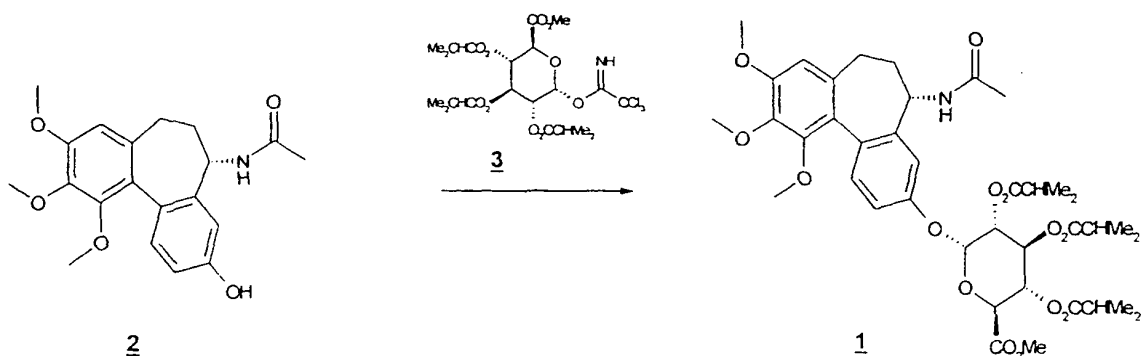
Yield : 68 %

¹H NMR spectrum (DMSO-d₆, CF₃CO₂D) : 1.88 (m, 1H) ; 1.89 (s, 3H) ; 2.08 (m, 1H) ; 2.15 (m, 1H) ; 2.52 (m, 1H, signal obscured partially by DMSO peak) ; 3.25-3.36 (m, 3H) ; 3.44 (t, 1H) ; 3.51 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 3.91 (d, 1H) ; 4.50 (m, 1H) ; 5.03 (d, 1H) ; 6.77 (s, 1H) ; 6.98 (s, 1H) ; 7.00 (d, 1H) ; 7.26 (d, 1H).

MS - ESI : 534 [MH]⁺

Elemental analysis	Found	C 55.7	H 6.1	N 2.5
C ₂₆ H ₃₁ NO ₁₁ ; 1.5 H ₂ O	Requires	C 56.0	H 5.9	N 2.6%

The starting material was prepared as follows :



Freshly distilled boron trifluoride-diethyl ether (0.22 ml ; 1.7 mmol) was added at 0°C under argon atmosphere to a stirred solution of *N*-acetyl-colchicinol (2) (303 mg ; 0.85 mmol)

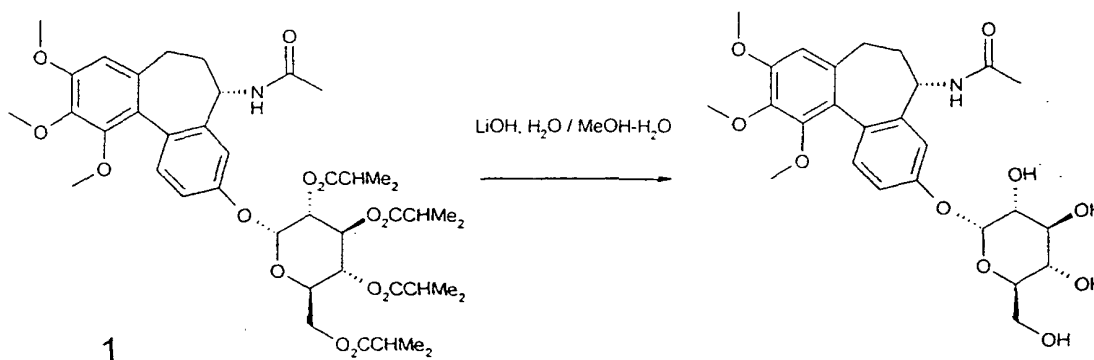
and methyl (trichloroacetimidoyl 2, 3, 4-tri-O-isobutyryl- α -D-glucopyranosid) uronate (3) (955 mg ; 1.7 mmol), (THL 36, 8601, 1995), in dichloromethane (8 ml). The mixture was stirred at 0°C for 15 minutes and then at ambient temperature for 2 hours. The reaction mixture was diluted with dichloromethane, washed with aqueous saturated sodium hydrogen carbonate, water, then dried (MgSO_4) and evaporated. The residue was purified by flash chromatography eluting with a 0 to 35 % gradient of dichloromethane/ether to give, after evaporation, (1) as a light yellow-green foam.

Yield : 82 %

^1H NMR spectrum ($\text{DMSO-d}_6 + \text{CD}_3\text{CO}_2\text{D}$) : 1.01-1.06 (m, 18H) ; 1.87 (m, 1H) ; 1.89 (s, 3H) ; 2.13 (m, 1H) ; 2.26 (m, 1H) ; 2.50 (m, 4H, signal obscured partially by DMSO peak) ; 3.50 (s, 3H) ; 3.65 (s, 3H) ; 3.78 (s, 3H) ; 3.83 (s, 3H) ; 4.58 (m, 1H) ; 4.74 (d, 1H) ; 5.11 (t, 1H) ; 5.17 (d, 1H) ; 5.60 (t, 1H) ; 5.73 (d, 1H) ; 6.77 (s, 1H) ; 6.94 (s, 1H) ; 6.95 (d, 1H) ; 7.28 (d, 1H) ; 8.37 (d, 1H).

MS - ESI : 758 $[\text{MH}]^+$

Example 45



(2*R*,3*R*,4*S*,5*R*,6*R*)-2-[(5*S*)-5-(Acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]oxy-3,5-bis(isobutyryloxy)-6-[(isobutyryloxy)methyl]tetrahydro-2*H*-pyran-4-yl 2-methylpropanoate (1) (304 mg ; 0.38 mmol) and H_2O (0.25 ml) were added to a 0.48M solution of lithium hydroxide monohydrate in methanol (6 ml). The mixture was stirred at ambient temperature for 6 hours. After removal of the methanol by evaporation, the remaining aqueous solution was adjusted to pH6.2 with 2N hydrochloric acid. The resulting heterogeneous solution was deposited on a

column of HP20 SS resin (35 ml) for purification, eluting with a 0 - 60 % gradient of methanol/water. After concentration and freeze drying *N*-((5*S*)-9,10,11-trimethoxy-3-[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl]oxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl)acetamide was obtained as a white solid (180 mg).

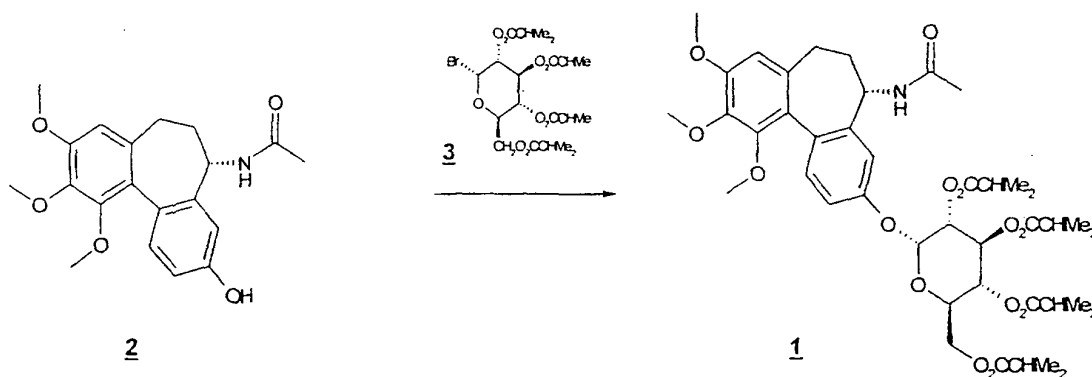
Yield : 84 %

¹H NMR spectrum (DMSO-d₆, CF₃CO₂D) : 1.88 (m, 1H) ; 1.90 (s, 3H) ; 2.10 (m, 1H) ; 2.18 (m, 1H) ; 2.52 (m, 1H, signal obscured partially by DMSO peak) ; 3.21-3.37 (m, 4H) ; 3.51 (s, 3H) ; 3.48-3.58 (m, 1H) ; 3.74-3.81 (m, 1H) ; 3.80 (s, 3H) ; 3.84 (s, 3H) ; 4.50 (m, 1H) ; 4.92 (d, 1H) ; 6.78 (s, 1H) ; 6.98 (d, 1H) ; 7.00 (dd, 1H) ; 7.26 (d, 1H) ; 8.36 (d, 1H).

MS - ESI : 542 [MNa]⁺

Elemental analysis	Found	C 55.3	H 6.6	N 2.6
C ₂₆ H ₃₃ NO ₁₀ 2.6 H ₂ O	Required	C 55.1	H 6.8	N 2.5%

15 The starting material was prepared as follows:



N-Benzyltributylammomium bromide (523 mg ; 1 mmol) and *N*-acetyl-colchicinol (2) (357 mg ; 1 mmol) in a 1.25*N* aqueous solution of sodium hydroxide were added at 0°C to a solution of the (2*R*,3*R*,4*S*,5*S*,6*R*)-2-bromo-3,5-bis(isobutyryloxy)-6-[(isobutyryloxy)methyl]tetrahydro-2*H*-pyran-4-yl 2-methylpropanoate (3) (523 mg ; 1 mmol), (J. Chem. Soc. Perkins Trans. 1 1995 p 577), in trichloromethane (2 ml). After 1 hour the reaction mixture was stirred at ambient temperature. Additional reagent (3) (250 mg ; 0.48 mmol and 1.33 mg ; 0.33 mmol) and 1.25*N* sodium hydroxide (0.2 ml and 0.1 ml) were added

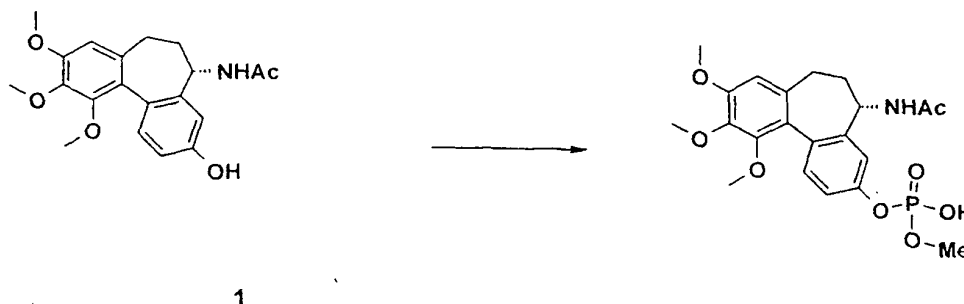
to the reaction mixture after 6 hours at ambient temperature and then again after a further 14 hours at ambient temperature. After a total of 24 hours, the reaction mixture was diluted with dichloromethane, washed successively with water, brine and then dried (MgSO_4). After removal of the solvent, the residue was purified by flash chromatography eluting with
 5 dichloromethane/ether (8/2 to 6/4) to give (1) (320 mg) as a foam.

Yield : 40 %

^1H NMR spectrum (DMSO-d_6) : 1.00-1.11 (m, 24H) ; 1.88 (m, 1H) ; 1.89 (s, 3H) ; 2.08 (m, 1H) ; 2.21 (m, 1H) ; 2.46-2.66 (m, 5H, signal obscured partially by DMSO peak) ; 3.48 (s, 3H) ; 3.77 (s, 3H) ; 3.83 (s, 3H) ; 4.16-4.24 (m, 2H) ; 4.32 (m, 1H) ; 4.47 (m, 1H) ; 5.08 (m,
 10 2H) ; 5.54 (t, 1H) ; 5.67 (d, 1H) ; 6.77 (s, 1H) ; 6.92 (d, 1H) ; 6.95 (dd, 1H) ; 7.25 (d, 1H) ; 8.38 (d, 1H).

MS-ESI : 800 $[\text{MH}]^+$

Example 46



15

A solution of *N*-acetyl-colchicinol (1) (0.45 g ; 1.26 mmol) in THF (40 ml) under argon was cooled to 0°C and treated with a 1.0M solution of lithiumHMDS in THF (1.39 ml ; 1.39 mmol). The mixture was stirred at 0°C for 1 hour and then added in portions over about
 20 15 minutes to a solution of methyl dichlorophosphate (625 μl ; 4.16 mmol) in THF (150 ml). The mixture was stirred at ambient temperature for 15 minutes. After addition of water (200 ml) the THF was removed by evaporation. After removal of the insoluble material by filtration, the filtrate was purified on HP20 SS resin eluting with a gradient of 0-60% methanol/water. The appropriate fractions were freeze-dried to give (5*S*)-5-(acetylamino)-
 25 9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl methyl hydrogen phosphate as a white solid (391 mg).

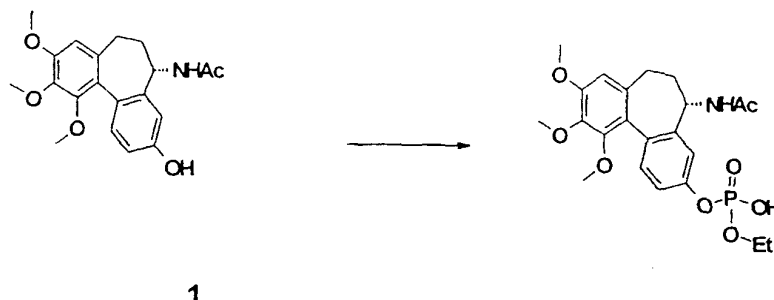
Yield : 69%

¹H NMR spectrum (DMSO d₆ ; CF₃CO₂D) : 1.89 (s, 3H) ; 1.9 (m, 1H) ; 2.05 (m, 1H) ; 2.18 (m, 1H) ; 2.5 (m, 1H, signal obscured partially by DMSO peak) ; 3.53 (s, 3H) ; 3.73 (d, 3H) ; 3.79 (s, 3H) ; 3.84 (s, 3H) ; 4.51 (m, 1H) ; 6.79 (s, 1H) ; 7.14 (d, 1H) ; 7.15 (s, 1H) ; 7.32 (d, 5 1H) ; 8.46 (d, 1H).

MS-ESI : 451 [MH]⁺

Elemental analysis :	Found	C 54.1	H 5.9	N 3.1
C ₂₁ H ₂₆ NO ₈ P ; 0.7 H ₂ O	Requires	C 54.2	H 6.0	N 3.0%

10 Example 47



A solution of *N*-acetyl-colchicinol (1) (0.36 g ; 1.0 mmol) in THF (40 ml) under argon was cooled to 0°C and treated with a 1.0M solution of lithiumHMDS in THF (1.1 ml ; 1.1 15 mmol). The mixture was stirred at 0°C for 1 hour and then added in portions over about 2 hours to a solution of ethyl dichlorophosphate (400 µl ; 3.3 mmol) in THF (150 ml). The mixture was stirred at ambient temperature for 15 minutes. After addition of water (200 ml) the THF was removed by evaporation. After removal of the insoluble material by filtration, the filtrate was purified on HP20 SS resin eluting with a gradient of 0-60% methanol/water. 20 The appropriate fractions were freeze-dried to give (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl ethyl hydrogen phosphate as a white solid (259 mg).

Yield : 56%

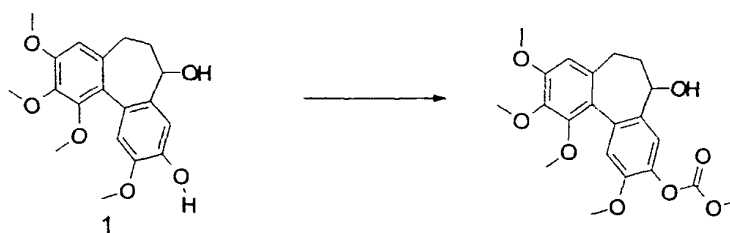
¹H NMR spectrum (DMSO d₆ ; CF₃CO₂D) : 1.25 (dt, 3H) ; 1.89 (s, 3H) ; 1.9 (m, 1H) ; 2.05 (m, 1H) ; 2.19 (m, 1H) ; 2.5 (m, 1H, signal obscured partially by DMSO peak) ; 3.53 (s, 3H) ; 25

3.79 (s, 3H) ; 3.85 (s, 3H) ; 4.09 (m, 2H) ; 4.52 (m, 1H) ; 6.80 (s, 1H) ; 7.13 (d, 1H) ; 7.15 (s, 1H) ; 7.32 (d, 1H) ; 8.45 (d, 1H).

MS-ESI : 466 [MH]⁺

Elemental analysis :	Found	C 54.6	H 6.0	N 3.0
5 C ₂₂ H ₂₈ NO ₈ P; 1.0 H ₂ O	Requires	C 54.7	H 6.3	N 2.9%

Example 48



10

Triethylamine (140 μ l ; 1.0 mmol) and methyl chloroformate (80 μ l ; 1.0 mmol) were added to a solution of 5-hydroxy-2,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[*a,c*]cyclohepten-3-ol (1) (0.18 g ; 0.5 mmol) in THF (10 ml). The mixture was stirred at ambient temperature overnight. After removal of the insoluble material by filtration the residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate/hexanes (5 to 60% ethyl acetate) to give **5-hydroxy-2,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[*a,c*]cyclohepten-3-yl methyl carbonate** as a hard oil/white solid (163 mg).

20 Yield : 81%

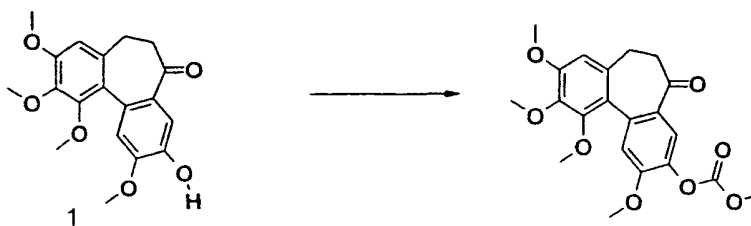
¹H NMR spectrum (CDCl₃) : 1.89 (m, 1H) ; 2.39 (m, 2H) ; 2.54 (m, 1H) ; 3.61 (s, 3H) ; 3.87 (s, 3H) ; 3.91 (s, 3H) ; 3.92 (s, 3H) ; 3.93 (s, 3H) ; 4.56 (m, 1H) ; 6.59 (s, 1H) ; 7.15 (s, 1H) ; 7.45 (s, 1H).

MS-ESI : 427 [MNa]⁺

25

Example 49

- 105 -



Triethylamine (35 μ l ; 0.225 mmol) and methyl chloroformate (20 μ l ; 0.225 mmol) were added to a solution of 3-hydroxy-2,9,10,11-tetramethoxy-6,7-dihydro-5H-

5 dibenzo[*a,c*]cyclohepten-5-one (1) (0.052 g ; 0.15 mmol) in THF (5 ml). The mixture was stirred at ambient temperature for 5 hours. After removal of the insoluble material by filtration the residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate/hexanes (0 to 100% ethyl acetate) to give **methyl 2,9,10,11-tetramethoxy-5-oxo-6,7-dihydro-5H-dibenzo[*a,c*]cyclohepten-3-yl carbonate** as a white solid (57 mg).

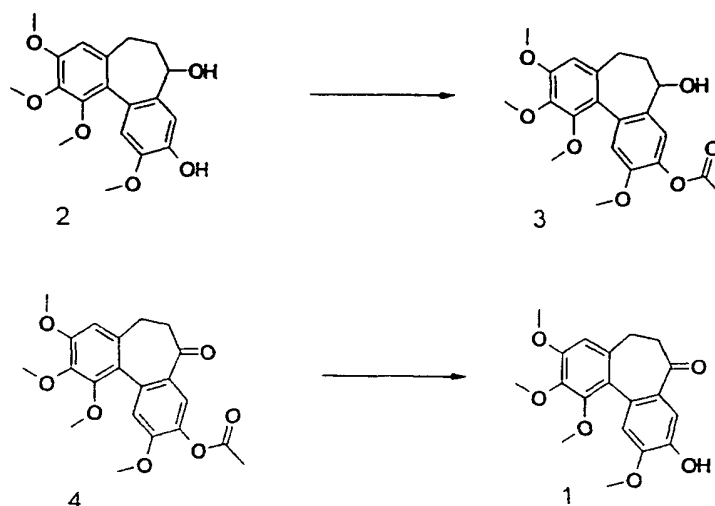
Yield : 95%

¹H NMR spectrum (CDCl₃) : 2.69 (m, 1H) ; 2.85 (m, 1H) ; 2.97 (m, 1H) ; 3.16 (m, 1H) ; 3.53 (s, 3H) ; 3.93 (s, 3H) ; 3.94 (s, 3H) ; 3.94 (s, 3H) ; 3.95 (s, 3H) ; 6.64 (s, 1H) ; 7.24 (s, 1H) ; 7.47 (s, 1H).

15 MS-ESI : 403 [MH]⁺

Elemental analysis :	Found	C 62.0	H 5.5
C ₂₁ H ₂₂ O ₈ ; 0.2 H ₂ O	Requires	C 62.1	H 5.6%

The starting material was prepared as follows:



Triethylamine (1.05 ml ; 7.5 mmol) and acetyl chloride (540 μ l ; 7.5 mmol) were added to a solution of 5-hydroxy-2,9,10,11-tetramethoxy-6,7-dihydro-5H-

- 5 dibenzo[*a,c*]cyclohepten-3-ol (2) (1.05 g ; 3.0 mmol) in THF (50 ml). The mixture was stirred at ambient temperature overnight. After removal of the insoluble material by filtration the residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate/hexanes (0 to 100% ethyl acetate) to give methyl 5-hydroxy-2,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[*a,c*]cyclohepten-3-yl carboxylate (3) as a white solid
10 (880 mg).

Yield : 76%

^1H NMR spectrum (CDCl_3) : 1.89 (m, 1H) ; 2.34 (s, 3H) ; 2.38 (m, 2H) ; 2.53 (m, 1H) ; 3.61 (s, 3H) ; 3.84 (s, 3H) ; 3.90 (s, 3H) ; 3.91 (s, 3H) ; 4.55 (m, 1H) ; 6.59 (s, 1H) ; 7.14 (s, 1H) ; 7.35 (s, 1H).

- 15 MS-ESI : 411 [MNa] $^+$

Elemental analysis :	Found	C 65.0	H 6.3
$\text{C}_{21}\text{H}_{24}\text{O}_7$	Requires	C 64.9	H 6.2%

- A solution of (3) (0.776 g ; 2.0 mmol) in dichloromethane (30 ml) was added to a solution of Collins Reagent (3.1 g ; 12.0 mmol) in dichloromethane (30 ml). The mixture was
20 stirred at ambient temperature for 30 minutes. After removal of the insoluble material by filtration the filtrate was washed with 2N hydrochloric acid, then brine and dried over MgSO_4 . The residue was purified by flash chromatography eluting with increasingly polar mixtures of

ethyl acetate/hexanes (0 to 60% ethyl acetate) to give methyl 5-oxo-2,9,10,11-tetramethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl carboxylate (4) as a white solid (706 mg).

Yield : 91%

¹H NMR spectrum (CDCl₃) : 2.34 (s, 3H) ; 2.64 (m, 1H) ; 2.82 (m, 1H) ; 2.93 (m, 1H) ; 3.14 (m, 1H) ; 3.50 (s, 3H) ; 3.88 (s, 3H) ; 3.91 (s, 3H) ; 3.92 (s, 3H) ; 6.61 (s, 1H) ; 7.20 (s, 1H) ; 7.36 (s, 1H).

MS-ESI : 387 [MH]⁺

Elemental analysis :	Found	C 65.6	H 6.0
C ₂₁ H ₂₂ O ₇	Requires	C 65.3	H 5.7%

10 Water (10 ml) and saturated aqueous sodium hydrogen carbonate (10 ml) were added to a solution of (4) (0.58 g ; 1.5 mmol) in methanol (50 ml). The mixture was stirred at ambient temperature overnight. After dilution with ethyl acetate the organic phase was washed with 2N hydrochloric acid, then brine and dried over MgSO₄. The residue was triturated with ether and hexanes to give (1) as a white solid (441 mg).

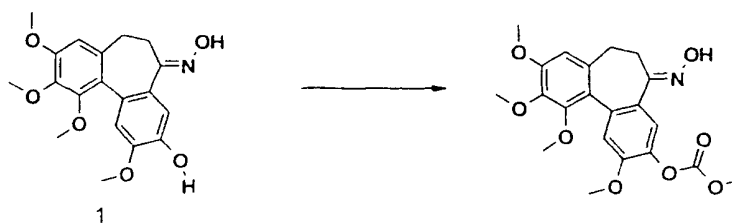
15 Yield : 85%

¹H NMR spectrum (CDCl₃) : 2.61 (m, 1H) ; 2.80 (m, 1H) ; 2.91 (m, 1H) ; 3.06 (m, 1H) ; 3.45 (s, 3H) ; 3.88 (s, 3H) ; 3.88 (s, 3H) ; 3.91 (s, 3H) ; 5.73 (s br, 1H) ; 6.58 (s, 1H) ; 7.09 (s, 1H) ; 7.17 (s, 1H).

MS-ESI : 345 [MH]⁺

20 Elemental analysis :	Found	C 65.52	H 6.10
C ₁₉ H ₂₀ O ₆ ; 0.2 H ₂ O	Requires	C 65.58	H 5.91

Example 50



Triethylamine (18 μ l ; 0.12 mmol) and methyl chloroformate (10 μ l ; 0.12 mmol) were added to a solution of 5-(hydroxyimino)-2,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[*a,c*]cyclohepten-3-ol (1) (0.035 g ; 0.1 mmol) in THF (3 ml). The mixture was stirred at ambient temperature overnight. After removal of the insoluble material by filtration the residue was purified by flash chromatography eluting with increasingly polar mixtures of ethyl acetate/hexanes (0 to 100% ethyl acetate) to give 5-(hydroxyimino)-2,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[*a,c*]cyclohepten-3-yl methyl carbonate (E isomer) as a white solid (22 mg), followed by the second (Z) isomer (7 mg).

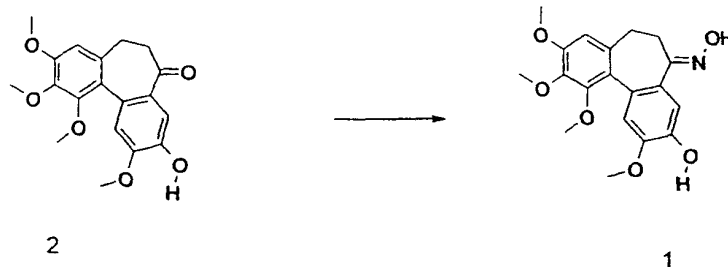
Yield : 54%

¹H NMR spectrum (CDCl₃) : 2.59 (m, 1H) ; 2.82 (m, 2H) ; 3.20 (m, 1H) ; 3.51 (s, 3H) ; 3.88 (s, 3H) ; 3.90 (s, 3H) ; 3.91 (s, 3H) ; 3.93 (s, 3H) ; 6.59 (s, 1H) ; 7.21 (s, 1H) ; 7.26 (s, 1H) ; 8.61 (br s, 1H).

MS-ESI : 418 [MH]⁺

Elemental analysis :	Found	C 58.1	H 5.7	N 3.0
C ₂₁ H ₂₃ NO ₈ ; 0.8 H ₂ O	Requires	C 58.4	H 5.7	N 3.2%

The starting material was prepared as follows :



20

Hydroxylamine hydrochloride (70 mg ; 1.0 mmol) was added to a solution of 3-hydroxy-2,9,10,11-tetramethoxy-6,7-dihydro-5H-dibenzo[*a,c*]cyclohepten-5-one (2) (0.172 g ; 0.5 mmol) in pyridine (3.0 ml). The mixture was stirred at ambient temperature overnight. After dilution with 2N hydrochloric acid and extraction with ethyl acetate, the organic phase was washed with 2N hydrochloric acid, then brine and dried over MgSO₄. The residue was triturated with ether and hexanes to give (1) (a 3:1 mixture of E:Z isomers) as a white solid (170 mg).

Yield : 95%

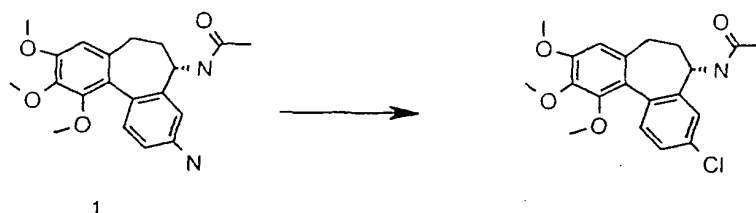
¹H NMR spectrum (CDCl₃), major isomer : 2.56 (m, 1H) ; 2.66-2.9 (m, 2H) ; 3.18 (m, 1H) ; 3.45 (s, 3H) ; 3.86 (s, 3H) ; 3.88 (s, 3H) ; 3.89 (s, 3H) ; 6.55 (s, 1H) ; 7.08 (s, 1H) ; 7.24 (s, 1H).

5 MS-ESI : 360 [MH]⁺

Elemental analysis :	Found	C 62.6	H 6.3	N 3.6
C ₁₉ H ₂₁ NO ₆ ; 0.3 H ₂ O	Requires	C 62.6	H 6.0	N 3.8%

Example 51

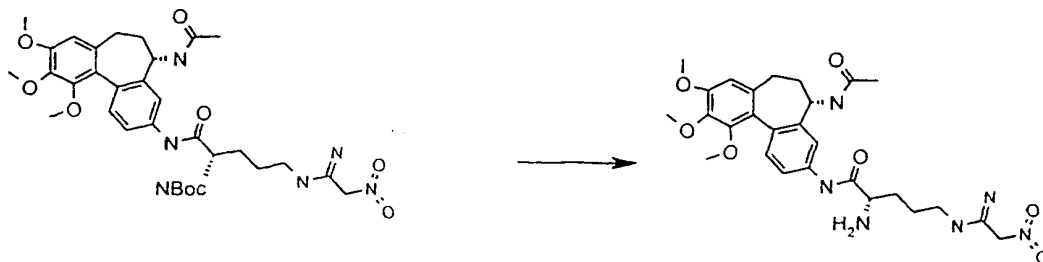
10



A solution of *N*-[(5*S*)-3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (0.712 g ; 2 mmol) in ethanol (3.75 ml) and 36% hydrochloric acid (1.57 ml) was slowly added into a mixture of ice (6 ml) and 36% hydrochloric acid (1.57 ml). At 0°C a solution of sodium nitrite (0.14 g ; 2 mmol) in water (0.25 ml) was added. The mixture was stirred at 0°C for 1 hour and then transferred into a separate flask containing a solution of copper(I) chloride (0.218 g ; 2.2 mmol) in water (0.35 ml) and 36% hydrochloric acid (0.4 ml). The resulting mixture was stirred at 30°C for 30 minutes and extracted with toluene/ethyl acetate (50/50). The organic phase was washed with water, dilute sodium hydroxide, and saturated sodium chloride solution, then dried and the volatiles were removed by evaporation. The residue was purified by flash chromatography eluting with ethyl acetate to give *N*-[(5*S*)-3-chloro-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide.

25 Yield : 46%.

¹H NMR Spectrum (DMSO-d₆) : 1.89 (s, 3H) ; 1.90 (m, 1H) ; 2.02 (m, 1H) ; 2.15 (m, 1H) ; 2.5 (m, 1H) ; 3.50 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 4.52 (m, 1H) ; 6.80 (s, 1H) ; 7.35 (m, 3H) ; 8.43 (d, 1H).

MS-ESI : 398 [MNa]⁺**Example 52**

5

A solution of (2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]-2-(*N*-*tert*butoxycarbonylamino)-5-[(2-nitroethanimidoyl)amino]pentanamide (1) (0.15 g, 0.28 mmol) in dichloromethane (2 ml) was treated at 0°C with TFA (2 ml). The mixture was stirred at ambient temperature for 2 hours and evaporated. The residue was taken up in methanol/dichloromethane and evaporated to give an oil which was triturated in ether to give (2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]-2-amino-5-[(2-nitroethanimidoyl)amino]pentanamide as a solid.

15 Yield : 95 %

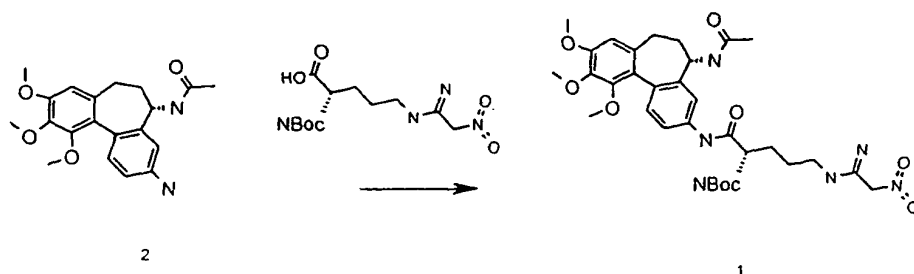
¹H NMR spectrum (DMSO-d₆) : 1.60 (m, 2H) ; 1.83 (m, 2H) ; 1.90 (s, 3H) ; 1.92 (m, 1H) ; 2.06 (m, 1H) ; 2.20 (m, 1H) ; 2.5 (m, 1H ; signal obscured by DMSO Peak) ; 3.22 (m, 2H) ; 3.50 (s, 3H) ; 3.79 (s, 3H) ; 3.85 (s, 3H) ; 3.95 (m, 1H) ; 4.48 (m, 1H) ; 6.80 (s, 1H) ; 7.32 (d, 1H) ; 7.45 (d, 1H) ; 7.75 (dd, 1H) ; 8.45 (d, 1H).

20 MS - ESI : 558 [MH]⁺

Elemental analysis	Found	C 48.1	H 5.7	N 13.2
C ₂₆ H ₃₅ N ₇ O ₇ ; 1.4 TFA; 0.5 methanol	Requires	C 48.0	H 5.3	N 13.4%

The starting material was prepared as follows:

25

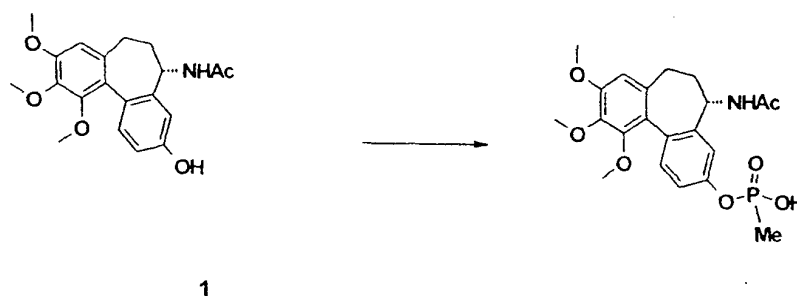


A solution of *N*-[(5*S*)-3-amino-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide (2) (0.45 g ; 1.26 mmol), *N*α-*tert*-butoxycarbonyl-ω-nitro-L-arginine (50.402 g ; 1.26 mmol), EDCI (0.312 g ; 1.63 mmol) and DMAP (0.03 g ; 0.25 mmol) in dichloromethane (18 ml) was stirred at ambient temperature overnight. After addition of water (2 ml) and extraction, the organic phase was evaporated to give an oil which was purified by flash chromatography eluting with ethyl acetate/methanol (95/5) to give (1). Yield : 28 %

¹H NMR (DMSO-d₆) : 1.38 (m, 2H) ; 1.40 (s, 9H) ; 1.60 (m, 2H) ; 1.90 (s, 3H) ; 1.91 (m, 1H) ; 2.15 (m, 2H) ; 2.5 (m, 1H, signal obscured by DMSO peak) ; 3.20 (m, 2H) ; 3.48 (s, 3H) ; 3.79 (s, 3H) ; 3.84 (s, 3H) ; 4.13 (m, 1H) ; 4.50 (m, 1H) ; 6.80 (s, 1H) ; 7.10 (d, 1H) ; 7.27 (d, 2H) ; 7.55 (s, 1H) ; 7.62 (d, 1H) ; 8.40 (d, 1H).

MS - ESI : 658 [MH]⁺

Example 53



A solution of *N*-acetyl-colchicinol (0.36 g ; 1.0 mmol) in THF (40 ml) under argon was cooled to 0°C and treated with a 1.0M solution of lithiumHMDS in THF (1.1 ml ; 1.1 mmol). The mixture was stirred at 0°C for 1 hour and then added in portions over about 2

hours to a solution of methylphosphonic dichloride (0.53 mg ; 4.0 mmol) in THF (150 ml). The mixture was stirred at ambient temperature for 15 minutes. After addition of water (200 ml) the THF was removed by evaporation. After removal of the insoluble material by filtration, the filtrate was purified on HP20 SS resin eluting with a gradient of 0-60% methanol/water. The methanol was removed by evaporation and the mixture was adjusted to pH7.14 with sodium hydroxide (0.1 M). The appropriate fractions were freeze-dried to give (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl hydrogen methylphosphonate as a beige solid (180 mg).

Yield : 41%

¹H NMR spectrum (DMSO *d*₆ ; CF₃CO₂D) : 1.53 (d, 3H) ; 1.88 (s, 3H) ; 1.9 (m, 1H) ; 2.06 (m, 1H) ; 2.16 (m, 1H) ; 2.5 (m, 1H, signal obscured partially by DMSO peak) ; 3.52 (s, 3H) ; 3.78 (s, 3H) ; 3.84 (s, 3H) ; 4.51 (m, 1H) ; 6.79 (s, 1H) ; 7.13 (s, 1H) ; 7.14 (d, 1H) ; 7.30 (d, 1H) ; 8.45 (d, 1H).

MS-ESI : 458 [MNa]⁺

Example 54

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)	<u>Tablet I</u>	<u>mg/tablet</u>
	Compound X	100
	Lactose Ph.Eur.....	182.75
25	Croscarmellose sodium	12.0
	Maize starch paste (5% w/v paste)	2.25
	Magnesium stearate	3.0
(b)	<u>Tablet II</u>	<u>mg/tablet</u>
30	Compound X	50
	Lactose Ph.Eur.....	223.75
	Croscarmellose sodium	6.0

		Maize starch.....	15.0
		Polyvinylpyrrolidone (5% w/v paste).....	2.25
		Magnesium stearate	3.0
	(c)	<u>Tablet III</u>	<u>mg/tablet</u>
5		Compound X	1.0
		Lactose Ph.Eur.....	93.25
		Croscarmellose sodium	4.0
		Maize starch paste (5% w/v paste)	0.75
		Magnesium stearate	1.0
10			
	(d)	<u>Capsule</u>	<u>mg/capsule</u>
		Compound X	10
		Lactose Ph.Eur.....	488.5
		Magnesium stearate	1.5
15			
	(e)	<u>Injection I</u>	<u>(50 mg/ml)</u>
		Compound X	5.0% w/v
		1M Sodium hydroxide solution.....	15.0% v/v
		0.1M Hydrochloric acid	
20		(to adjust pH to 7.6)	
		Polyethylene glycol 400	4.5% w/v
		Water for injection to 100%	
	(f)	<u>Injection II</u>	<u>10 mg/ml)</u>
25		Compound X	1.0% w/v
		Sodium phosphate BP.....	3.6% w/v
		0.1M Sodium hydroxide solution.....	15.0% v/v
		Water for injection to 100%	
30	(g)	<u>Injection III</u>	<u>(1mg/ml.buffered to pH6)</u>
		Compound X	0.1% w/v
		Sodium phosphate BP.....	2.26% w/v

Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection to 100%	

Note

- 5 The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

Year	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	